IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC, Plaintiffs, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 06-286-GMS **REDACTED – PUBLIC VERSION**

DEFENDANT BARR LABORATORIES, INC.'S PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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INTRODUCTION

Barr is entitled to a judgment of patent noninfringement and invalidity. Aventis obtained patents that never should have issued and is now asserting them against Barr for trying to sell a cheaper, generic version of Nasacort AQ®, a nasal spray to treat nasal allergies.

Barr's nasal spray, however, does not infringe any of the asserted patent claims because, among other reasons, it does not reach the frontal sinus, which this Court has ruled is required by every asserted claim. The frontal sinus is an isolated part of the tortuous nasal cavity.

Aventis has not even tested whether Barr's product reaches the frontal sinus, much less proven that it meets that claim limitation. That alone should end this case as a matter of law.

Barr's product also does not infringe because it does not have the claimed viscosity profile after being sprayed into the nose. According to Aventis' claims, the accused nasal spray must return to its resting, in-the-bottle viscosity *after* being shaken and then sprayed into the nasal cavity. But Barr's product comes nowhere close to meeting that limitation. Aventis ignores the reality that it can take *hours and hours* for liquids to return to their resting or "unsheared" viscosity even when standing still in a sealed bottle at room temperature. Aventis thus cannot prove – and has not even attempted to prove – that Barr's product does so during the *30 minutes* or so it remains in the nasal cavity, which is a warm, moist environment full of nasal liquids, moving air and rapidly-beating cilia that *reduce* viscosity while quickly removing unwanted substances, such as bacteria and excess mucus.

Aventis' claims are also invalid for several reasons. First, the claims are invalid for obviousness under Section 103.

That is not a patentable invention under *KSR*, where the Supreme Court held that obviousness is now judged under "an expansive and flexible approach" driven by "common sense," and thus, patentability requires "more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007). In a huge majority of obviousness decisions since *KSR*, the Federal Circuit has found the claimed invention obvious, repeatedly overturning jury verdicts, bench verdicts, and summary judgment rulings rejecting obviousness challenges.[1] Thus, Aventis' patents on a completely standard formulation for a nasal spray, which merely copies and tweaks prior art formulations, cannot survive *KSR*.

Second, Aventis' patents are invalid for lack of enablement under Section 112. Not only is Barr's product unable to reach the frontal sinus,

And nothing in the specification teaches anyone how to

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[1] *Agrizap, Inc. v. Woodstream Corp.*, Nos. 2007-1415, 2007-1421, 2008 WL 819757, at *6 (Fed. Cir. Mar. 28, 2008) (reversing jury verdict and holding patent obvious); *Erico Int'l Corp. v. Vutec Corp.*, 516 F.3d 1350, 1356-57 (Fed. Cir. 2008) (vacating grant of preliminary injunction and holding that accused infringer established substantial likelihood of success in showing obviousness); *Translogic Tech., Inc. v. Hitachi, Ltd.*, Nos. 2005-1387, 2006-1333, 2007 WL 2973955, at *1 (Fed. Cir. Oct. 12, 2007) (vacating district court ruling and holding patent obvious); *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1262 (Fed. Cir. 2007) (finding patent obvious); *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1259 (Fed. Cir. 2007) (reversing district court and finding patent obvious); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302-03 (Fed. Cir. 2007) (finding patent *prima facie* obvious, lacking any unexpected properties or results, and thus, invalid); *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1320 (Fed. Cir. 2007) (finding patent obvious); *In re Trans Tex. Holdings Corp.*, 498 F.3d 1290, 1301 (Fed. Cir. 2007) (same); *In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1382 (Fed. Cir. 2007) (same); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1367 (Fed. Cir. 2007) (reversing jury verdict and finding patent obvious); *Frazier v. Layne Christensen Co.*, 239 Fed. App'x 604, 609 (Fed. Cir. 2007) (finding patent obvious); *Pfizer, Inc. v. Synthon Holdings BV*, 227 Fed. App'x 903, 904 (Fed. Cir. 2007) (reversing district court and finding patent obvious); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) (affirming this Court's decision of patent obviousness); *Syngenta Seeds, Inc. v. Monsanto Co.*, 231 Fed. App'x 954, 959 (Fed. Cir. 2007) (finding patent obvious).

make a nasal spray that reliably reaches the frontal sinus,

Third, Aventis' patents are invalid for anticipation based on prior public use under Section 102.

That is an invalidating prior public use as a matter of law.

PROPOSED FINDINGS OF FACT

I. Aventis' Patents.

1. Aventis is asserting two patents – United States Patent Nos. 5,976,573 ("the '573 patent") and 6,143,329 ("the '329 patent") – which are directed to nasal sprays containing triamcinolone acetonide or "TAA." TAA is a prior art glucocorticosteroid typically used to treat nasal abnormalities such as allergic rhinitis (or nasal allergies). ('573 patent, col. 1:5-14; *see also id.* at cols. 12:59-16:25; SUF ¶¶ 98, 139.)

2. Both the '573 patent and '329 patent claim priority from an application filed on July 3, 1996. (SUF ¶¶ 8, 10, 11.) The two patents share essentially the same specification and list the same inventor, Soo-Il Kim. (SUF ¶¶ 8, 10, 13.)

3. Aventis' claimed nasal spray is a water-based suspension that purports to be "thixotropic," which refers to the viscosity of a liquid. A liquid is "thixotropic" if it has a high viscosity when resting and a low viscosity when shaken or "sheared" in preparation for spraying. (*E.g.*, '573 patent, col. 2:18-39.) In theory, a "thixotropic" liquid provides an advantage for nasal sprays if the suspension's viscosity increases after reaching the nasal cavity, which would enable

the active ingredient to remain in the nasal cavity for a longer time by resisting the nose's clearance mechanisms (*i.e.*, "mucociliary clearance"). ('573 patent, cols. 1:53-57; 2:19-39.)

4. For nasal sprays, pharmaceutical companies commonly create "thixotropic" formulations by using a suspending agent that is a mixture of microcrystalline cellulose ("MCC") and carboxymethylcellulose ("CMC"). ('573 patent, cols. 5:25-37, 13:26-43, Example 1; DX13; DX14; DX16; DX43.) This mixture was commercially available as Avicel® long before July 3, 1995 in at least two grades called Avicel® RC-591 and Avicel® CL-611. (SUF ¶¶ 174-177; DX20; DX21; DX22; DX42; DX60.)

II. The Development Of Nasacort AQ.

5. The '573 and '329 patents are listed with the Food and Drug Administration in the "Orange Book" in connection with NDA No. 20-468 for Nasacort AQ. (SUF ¶ 19; D.I. 1, Complaint, ¶ 12.)

A. TAA Is An Old Active Ingredient.

6. Nasacort AQ is a nasal spray containing TAA as the active ingredient and treats allergic rhinitis. (D.I. 1, Compl., ¶ 10.) The formulation of Nasacort AQ is disclosed in Example 1 of the '573 and '329 patents. ('573 patent, col. 9:5-25; DX25)

7. TAA is a glucocorticosteroid that was known to treat allergic rhinitis since at least 1991, long before July 1995. (SUF ¶¶ 98, 139; DX31; '573 patent, col. 1:30-35.) For example, Aventis' predecessor, Rhone Poulenc Rorer – which Barr refers to throughout as "Aventis" for simplicity – used TAA as early as 1991 in a product called Nasacort® Nasal Inhaler, which is a nasal aerosol containing TAA. (SUF ¶¶ 98, 139; DX31.) It was approved by FDA to treat seasonal and perennial allergic rhinitis. (SUF ¶¶ 98, 138; DX35; DX31; DX155; DX158.)

8. Before Aventis worked on the claimed nasal spray, the FDA had approved dozens of products containing TAA, including tablets, capsules, injectibles, nasal sprays, syrups, ointments, creams, lotions, and pastes. (*See* www.fda.gov.) Approved products with TAA included Aventis' own Nasacort Nasal Inhaler.

9. By the time Aventis filed its relevant patent application, there were also other nasal sprays on the market containing different glucocorticosteroids for the treatment of allergic rhinitis, including Beconase®, Beconase AQ®, Vancenase® and Vancenase AQ®, all of which contained beclomethasone dipropionate as the active ingredient, and Flonase, which contained fluticasone propionate as the active ingredient. (SUF ¶¶ 89, 95, 96, 138, 140, 141; DX14; DX354; DX355.)

B. Like Many Other Companies, Aventis Reformulated Its Old Nasal Spray To Remove Chorofluorocarbon.

10. Aventis developed Nasacort AQ as a reformulation of its old product – Nasacort Nasal Inhaler – which contained chlorofluorocarbon ("CFC") as a propellant. (DX15; DX33.)

11. Because CFC depletes the ozone, movements to eliminate CFCs, as well as other ozone-depleting substances, resulted in the promulgation in 1987 of the Montreal Protocol on Substances that Deplete the Ozone Layer, which called for the ban of production and consumption of CFCs in the United States by January 1, 1996, absent an annual approval of an essential use exemption by the parties to the Protocol. (DX143; DX13.)

12. While aerosol nasal sprays qualified for an essential use exemption, the pharmaceutical industry began searching for alternatives to CFC-based products as early as the late 1980s. (DX297; Kim Tr. at 26:12-13, 19-21, 27:3.)

13. The main alternative was an aqueous, or water-based, suspension that suspended the active ingredient in a viscous solution while still permitting the solution to disperse the solid

drug particles when sprayed. (DX38.) Many patients preferred the aqueous preparations to the CFC-based aerosols because they were more comfortable. (DX32; DX10; DX11; DX33; Kaliner Tr. at 130:8-132:4.)

14. As early as 1987, non-propellant, CFC-free, aqueous nasal sprays hit the market, including Beconase AQ and Vancenase AQ. (SUF ¶¶ 89, 101-106, 140, 141; DX14; DX26; DX27.)

15. The FDA approved a similar product, Flonase, in 1994 for the treatment of allergic rhinitis. Flonase was an aqueous nasal spray containing another glucocorticosteroid, fluticasone propionate. (SUF ¶¶ 89, 95, 99, 101-106; DX28.)

C. Aventis Formulated Its Claimed Nasal Spray By Copying The Ingredient List Of Prior Art Formulations With Only Minor Tweaks.

16. It was against this backdrop that Aventis began to develop Nasacort AQ.

. (DX33; DX35; DX36.)

17. For the active ingredient, '

the same dosing regimen as Nasacort Nasal Inhaler. (DX34; *see also* Alcorn Tr. at 128:24-130:14; Laverty Tr. at 56:5-57:4, 134:21-136:2.)

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(DX37; DX173; Kim Tr. at 106:11-25; Laverty Tr. at 48:14-49:19; DX185; DX186; DX187.)

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the same as the inactive ingredients in Beconase AQ, Vancenase AQ, and Flonase. (*Compare* DX37 *with* DX14; DX18; DX19.)

(*See, e.g.*, '573 patent, Example 1; DX25.)

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routine optimization with varying concentrations of MCC/CMC mixtures, which is what gives nasal sprays the thixotropic properties that allow the liquid to "suspend" the drug particles uniformly in the formulation while permitting the reduced viscosity through shaking and spray to deposit the active ingredient into parts of the nasal cavity. (DX34; DX24; *see also* Alcorn Tr. at 128:24-130:14; Laverty Tr. at 56:5-57:4, 134:21-136:2.)

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(DX34; DX24.)

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(DX34; DX24; DX174.)

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routine formulation, making known substitutions of ingredients from previously marketed products.

III. Aventis' Prior Public Use Of Nasacort AQ In Clinical Trials.

30. Aventis began publicly using the Nasacort AQ formulation long before filing its patent application in 1996. (SUF ¶¶ 8, 11.) Aventis has produced no evidence suggesting that

these public uses – large clinical trials – had anything to do with creating the purported invention and/or the proving that the claimed invention allegedly worked.

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41. two articles on them in *Clinical Therapeutics*. One paper, by Settipane, *et al.*, described the results of t seasonal allergic rhinitis. (SUF ¶¶ 4-6, 168, 211, 213; DX10.) The other paper,

by Kobayashi, *et al.*, described the results of on perennial allergic rhinitis. (SUF ¶¶ 4, 5, 7, 169, 212-213; DX11.)

42. Both papers disclose the use of an aqueous TAA nasal spray to treat seasonal or perennial allergic rhinitis. (SUF ¶¶ 218-219; DX10; DX11.) They disclose the safety and efficacy of a once-daily, 55 mcg/spray dose, for a total of 220 mcg/day. (DX10; DX11.)

43. These two papers, Settipane and Kobayashi, were both published before July 3, 1995 and qualify as prior art to the patents-in-suit under 35 U.S.C. § 102(b). (DX10; DX11; SUF ¶¶ 168-169.)

44. In addition, the patent applicants filed a sworn declaration in the USPTO informing the Patent Examiner that the product discussed in these articles and used in the clinical trials was the subject of the patents. (DX2; SUF ¶¶ 208-209; 213.)

45. FDA approved NDA No. 20-468 on or about May 20, 1996. (SUF ¶¶ 18; DX58.)

IV. Barr's ANDA Product.

46. On December 29, 2005, Barr filed ANDA No. 78-104 with FDA, requesting approval to make and sell a generic version of Nasacort AQ before the expiration of the '573 and '329 patents. (SUF ¶ 20.)

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48. Significantly, FDA has promulgated draft guidance documents that inform generic manufacturers that these nasal sprays should be "qualitatively the same and quantitatively essentially the same in formulation" to the branded drug. (DX263; DX323; DX264.)

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V. Asserted Patent Claims And Claim Construction.

50. Aventis has asserted claims 5-8, 21-24, 26-28 and 34-35 of the '573 patent and claims 13-16 and 23-26 of the '329 patent. (SUF ¶¶ 16-17.)

51. The asserted claims are composition and product claims ('573 patent claims 5-8; '329 patent claim 13) and method claims ('573 patent claims 21-24, 26-28, 34-35; '329 patent, claims 14-16, 23-26.)

52. The composition and product claims require an aqueous thixotropic pharmaceutical composition of TAA containing a number of excipients, including water, a mixture of MCC and CMC, benzalkonium chloride, EDTA, polysorbate 80 and dextrose. The composition should be propellant-free with a pH of about 4.5 to about 7.5.

53. '329 patent claim 13 further requires a precompression pump and associated vessel, as does dependent '573 patent claim 27. ('329 patent, claim 13; '573 patent, claim 27.)

54. Independent claim 5 of the '573 patent and its dependent claims call for specific concentration ranges of TAA and the claimed excipients and contain the claim term "odorless."

55. These claims also require the following specific thixotropic properties of the composition, which is commonly measured in terms of "centipoise:"

> (i) the viscosity of the composition in unsheared form is **about 400 to about 800 cp** [centipoise];
>
> (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition is **about 50 to about 200 cp** and such that the composition in the form of a mist flows readily into the nasal passages **for deposit on the mucosal surfaces of the nasal cavity**; and

> (iii) **in deposited form on the mucosal surfaces**, the viscosity of the composition is **about 400 to about 800 cp** and **such that it resists being cleared** from the mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity.

('573 patent, claim 5; '329 patent claim 26; *see also* '573 patent claim 35 (unsheared viscosity of "about 400 to about 1000 centipoises").)

56. The Court has construed the terms "for deposit on the mucosal surfaces of the nasal cavity" and "in deposited form on the mucosal surfaces" to require the medicament to be "deposited on all of the mucosal surfaces" of the nasal cavity, meaning "the mucous membranes that line, among other things, the anterior regions of the nose, the turbinates which overlie the concha, the maxillary sinuses, and the frontal sinus." (D.I. 130, ¶ 6.) By the parties' agreement, the Court has also construed the term "odorless" to mean "[o]dors that cause the user discomfort are absent." (D.I. 114, '573 patent, p. 4.)

57. The method claims claim methods of using an aqueous thixotropic pharmaceutical composition containing TAA to treat allergic rhinitis ('573 patent claim 21; '329 patent claim 14), methods of applying solid particles of TAA to the mucosal surfaces of the nasal cavity ('573 patent claim 34), and methods for delivering an aqueous thixotropic pharmaceutical composition containing TAA to the mucosal surfaces of the nasal cavity ('329 patent claim 25). Several claims require pharmaceutically effective amounts of TAA to remain on the mucosal surfaces of the nasal cavity for at least about an hour. ('573 patent claims 21-24, 26-28, 34-35.)

58. Every asserted claim contains the claim term "thixotropic." Where the claims do not specify the thixotropic properties, the Court has construed the term "thixotropic" to require the following properties:

> (i) In unsheared form, the composition is a gel in which the particles of medicament are dispersed and suspended substantially uniformly. The viscosity

of the composition in unsheared form is relatively high (*i.e.*, higher than the shear viscosity).

(ii) When subjected to shear, the viscosity of the composition is relatively low (*i.e.*, lower than the unsheared viscosity) and such that the composition in the form of a mist flows readily through the spray device for deposit on the mucosal surfaces of the nasal cavity, including at least the following parts of the nose: the anterior regions of the nose (frontal nasal cavities); the frontal sinus; the maxillary sinuses; and the turbinates which overlie the conchas of the nasal cavity.

(iii) In deposited form on the mucosal surfaces of the nasal cavity, the viscosity of the composition is relatively high (*i.e.*, it returns to its unsheared viscosity) and such that the composition resists being cleared from the nasal passages by the inherent mucocillary forces that are present in the nasal cavity.

('573 patent, cols. 2:28-38, 4:36-60; D.I. 130, ¶¶ 2-4, 6 & n.2.)

59. Thus, under the Court's construction, every asserted claim requires at least the following elements: (1) in deposited form in the nasal cavity, the composition returns to its unsheared viscosity or a viscosity of about 400 to about 800 or 1000 centipoise; (2) the composition resists mucociliary clearance or retains the TAA on the mucosal surfaces of the nasal cavity; and (3) the composition deposits on the frontal sinus.

VI. Neither Barr's ANDA Product, Nor Nasacort AQ Meets Each And Every Limitation Of Every Asserted Claim.

A. Barr's ANDA Product Does Not Return To Its Unsheared Viscosity Or To A Viscosity Of About 400 To About 800 Or 1000 Centipoise In Deposited Form.

60. Aventis has offered no evidence that Barr's ANDA product, in deposited form in the nasal cavity, returns to unsheared viscosity or to a viscosity in the range of about 400 to about 800 or 1000 centipoise.

61. The viscosity of Barr's ANDA product when deposited on the nasal mucosa has never been measured. And there is no known way to measure the viscosity of such a composition in deposited form on the nasal mucosa. (*See* Alcorn Tr. at 340:7-17; Kim Tr. at 116:23-117:8; Prud'homme Tr. at 178:3-10, 183:1-10.) All of the viscosity measurements

conducted on Barr's ANDA product or Nasacort AQ are *in vitro* measurements; that is, measurements taken on the materials when they were outside the human body. They were not *in vivo* measurements, meaning measurements taken on the materials when they were in the nasal cavity.

62. Furthermore, there is no reason to believe Barr's ANDA product would return to unsheared viscosity or to about 400 to about 800 or 1000 centipoise in deposited form on the nasal mucosa. In fact, there are many reasons to conclude it would not, including the following.

63. First, the nasal cavity is much warmer than room temperature. This is likely, by itself, to decrease the viscosity of the composition when it is deposited in the nasal cavity. (Prud'homme Tr. at 228:15-229:5.)

64. Second, the nasal cavity is moist. Anything sprayed on the nasal mucosa will be miscible with and continuously diluted by nasal secretions, making it unlikely that Barr's ANDA product will return to its unsheared viscosity in deposited form. (Lochhead Tr. at 107:8-15.)

65. Third, the mucosal surface of many of the epithelial cells present in the main nasal cavity contain hair-like projections, called cilia, which beat in a synchronized fashion and act to clear the secretions and any associated trapped particulate matter from the nasal cavity. The cilia act as shearing entities and may continue to shear Barr's ANDA product when it is sprayed into the nose, further preventing the composition from returning to its unsheared viscosity. (Lochhead Tr. at 111:24-112:4.)

66. Fourth,

Barr's ANDA product would likewise take days to recover unsheared viscosity. By the time it does, it is likely to have been cleared from the nasal mucosa by the rapid forces of mucociliary clearance.

67. Thus, no evidence exists to show that Barr's ANDA product would return to its unsheared viscosity in deposited form on the nasal mucosa, much less to the specific range of about 400 to about 800 or 1000 centipoise required by many claims.

B. The Composition Of Barr's ANDA Product Does Not Resist Mucociliary Clearance Or Retain TAA On The Nasal Mucosa.

68. As noted, all of the claims require that "the composition" – as opposed to the active ingredient itself – "resists being cleared from the mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity" or that it "retain[s]" "pharmaceutically effective amounts" of TAA on the nasal mucosa "for at least about an hour." Thus, an active ingredient by itself that resists clearance would not meet the claim limitations. Instead, the viscosity characteristics of the complete composition must be responsible for the slowed clearance.

69. Here, however, there is no evidence that the composition of Barr's ANDA product, rather than the active ingredient itself, resists mucociliary clearance or that it is responsible for the retention of TAA on the nasal mucosa.

70. The composition in which the TAA drug particles are suspended in Barr's product could be rapidly diluted and clear quickly while some drug particles remain adherent to the epithelial surface of the nasal mucosa. This would make it unlikely that the composition itself will resist mucociliary clearance or retain the TAA on the nasal mucosa.

71. The only evidence in this case relating to the retention of TAA on the nasal mucosa :

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74. Because that testing was never done,

cannot be relied on for an argument about whether the "viscosity of the composition" of Barr's ANDA product resists clearance or retains TAA on the nasal mucosa.

C. Barr's ANDA Product And Nasacort AQ Do Not Deposit On The Frontal Sinus, And Neither Product Is Retained There For At Least About An Hour.

75. Neither Barr's ANDA product nor Nasacort AQ deposits on the frontal sinus (as required by every claim) or is retained there for at least about an hour (as required by '573 patent claims 21-24, 26-28, and 34-35).

[2] Dr. Berridge maintains that the thixotropic nature of these formulations must be what is responsible for the retention of TAA on the nasal mucosa because he was informed of studies that show that normal mucociliary clearance takes place within 30 minutes. From those studies, none of which were conducted on formulations like these or on TAA particles, he infers that the thixotropic formulation must be keeping the TAA particles on the nasal mucosa because those particles remain there longer than 30 minutes. He has no basis for this inferential leap, however, nor does he have the requisite expertise in mucociliary clearance or the adequately controlled studies to make such a leap. (Berridge 2/21/08 Tr. at 120:23-121:7.)

76. The frontal sinus is in an isolated area of the nasal anatomy, which is hard to reach. The frontal sinus entrance is located between the middle and inferior turbinates (the middle meatus), behind a balloon shaped projection called the bulla ethmoidalis.

77. For mucus to drain from the frontal sinus to the middle meatus, it takes a tortuous route described by Daniels *et al.* as the frontal sinus drainage pathway (FSDP), which is the most complex and variable drainage path of any of the paranasal sinuses. (DX1.) The path is at a right angle to the direction of the airflow into the nose and to the direction of any substances sprayed into the nose.

78. In normal circumstances (assuming no surgery) and before the mucus membranes have been decongested, it is not possible even with an endoscope to examine this pathway up into the frontal sinus. (DX303.)

79. Actually reaching the frontal sinus with a spray would require the substance to pass into the narrow cleft of the middle meatus, pass the bulla ethmoidalis and make its way upwards and forwards through the FSDP and against the flow of the mucociliary pathway, which is travelling downwards and backwards.

80. The direction of the spray would literally need to turn back on itself and travel inwards and forwards to reach the frontal sinus. The flow of the nasal mucociliary pathway would propel any spray away from the frontal sinus rather than into it.

81. Therefore, a nasal spray like Nasacort AQ or Barr's ANDA product would be highly unlikely to enter the frontal sinus. (Kaliner Tr. at 102:7-103:5, 103:15-17, 105:21-110:4.)

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87. Dr. Berridge also believes that the 1996 study, the first study he conducted, and disclosed in the patents-in-suit, proves that Nasacort AQ deposits on the frontal sinus because 3-4% of the administered drug was observed in the regions he designated as frontal sinus regions. The 1996 study has significant problems, however, including the fact that it was not even intended to reliably measure the location of TAA deposit.

88. The 1996 study was the first study like this that anyone has ever conducted. It was primarily intended to "explore the feasibility and benefits of the application of PET to drug evaluation and design." (DX66.)

89. Moreover, due to limitations in the data analysis software, the investigators divided the head into 1.8 cm cubical regions of interest assigned to anatomical regions in order to analyze the data and assess where the drug deposited. (DX6.)

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91. Dr. Barry A. Siegel, a Barr expert, conducted a statistical comparison of the peak frontal sinus deposition which confirms the absence of any legitimate "finding" of deposit in the frontal sinus.

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thereby affecting the viscosity of the administered products and the deposition into the frontal sinus. (DX314.)

95. Dr. Berridge has no evidence to support this speculation.

He has no expertise in pharmaceutical formulation, no expertise in nasal anatomy and no knowledge of the effects of temperature on the spray pattern or deposition of these types of products. (Berridge 2/21/08 Tr. at 15:22-16:12, 209:17-210:14.)

96. He fashioned this "temperature hypothesis" after being retained as an expert in this case. (Berridge 2/21/08 Tr. at 166:19-22, 170:10-22.) It is therefore without foundation.

97. Critically for the infringement analysis,

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99. Finally, none of the subjects in Dr. Berridge's studies were allergic rhinitis patients. Rather, they were all healthy volunteers. In a congested patient suffering from allergic

rhinitis, whatever air flow reaches the frontal sinus would be more limited than in a healthy volunteer. (Kaliner Tr. at 276:2-22.)

100. In sum, the evidence shows that neither Nasacort AQ nor Barr's ANDA product would deposit on the frontal sinus of an individual when sprayed into the nasal cavity, nor would it remain there for at least about an hour.

VII. Prior Art.

A. Level Of Ordinary Skill In The Art.

101. Aventis' patents, entitled "Aqueous-Based Pharmaceutical Composition," are directed to an "aqueous pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual." ('573 patent, Abstract.)

102. Although some of the claims are directed to a method of treating allergic rhinitis, those claims are directed to the use of the claimed composition itself. As the patents' specification acknowledges, the use of TAA to treat allergic rhinitis was already known. ('573 patent, col. 1:29-32; *see also* DX15; DX64; SUF ¶¶ 98, 139.)

103. Instead, the relevant art relates generally to pharmaceutical formulation and, in particular, to the formulation of nasal sprays.

104. Accordingly, a person of ordinary skill in the relevant art has a degree in chemistry, biology, chemical engineering, or pharmaceutical sciences with significant experience in formulation development of nasal dosage forms, specifically, 3-5 years experience for a bachelor's degree, 1-3 years for a masters, and at least 1 year for a Ph.D. The person of ordinary skill in the art will also have the ability to operate independently on formulation activities. Without training in the pharmaceutical sciences, the person of ordinary skill in the art needs

additional training or education in toxicology, chemistry, pharmacology, and material sciences related to pharmaceutically relevant agents.

105. Nothing in the patents suggests that a person of skill in the art must have specific experience in thixotropic materials or the use of a Brookfield LVT viscometer. A person of ordinary skill in the art would only need to be able to understand these materials and instruments through his or her education and training. The mention of the Brookfield LVT viscometer in the patent specification ('573 patent, col. 5:18-24) is only relevant to inform the public of what the claimed viscosity ranges mean.

B. Scope And Content Of Prior Art.

106. Nasal products generally, including those that do not contain steroids, are within the scope of the prior art for the disputed patents. (Meltzer Tr. at 139:12-17, 144:14-144:22.)

107. References such as the Handbook of Pharmaceutical Excipients, Remington's Pharmaceutical Sciences and the Physician's Desk Reference, as well as published articles in pharmaceutical science journals, are also within the scope of the prior art. (Alcorn at 140:19-141:2, 180:18-181:4; DX173; Kim Tr. at 65:6-12, 105:24-106:25.)

1. Aqueous Nasal Spray Formulation.

108. Steroidal nasal products for the treatment of inflammatory abnormalities such as allergic rhinitis act topically. Therefore, the formulator's goal is to make a formulation that delivers the active ingredient to the nasal cavity without being cleared too quickly by normal mucociliary clearance. (DX38.)

109. Steroids, such as TAA, cannot be dissolved easily so they cannot simply be formulated into an aqueous solution. (DX41; DX353.) Instead, formulators might dissolve the steroid in a cosolvent such as polyethylene glycol or propylene glycol or might make aqueous

"suspensions" that carry the undissolved drug particles. (DX 38.) To ensure proper dosing from the spray pump in an aqueous suspension, the particles need to be carried homogenously throughout the suspension without aggregation or caking and, to the extent they settle, the particles must be easily redispersed with gentle shaking. (DX38.)

110. To accomplish that goal, formulators have long used "suspending agents," such as the mixture of CMC and MCC, to increase viscosity and, thus, reduce the tendency of the suspended particles to clump or settle to the bottom of the container. (DX38.)

111. Other excipients commonly used are: isotonicity adjusting agents like dextrose, antimicrobials like benzalkonium chloride, pH adjusting agents, wetting agents like polysorbate 80, and chelating agents like EDTA to prevent drug degradation. (*See* DX38.) EDTA was routinely employed in nasal preparations before July 1995. (*See* DX38; SUF ¶¶ 119-120, 129-136; DX46; DX47; DX14; DX17; DX12.)

112. Formulators have also long used pumps to administer compositions to the nose. In July 1995, there were two major pump manufacturers, Valois and Pfeiffer, both of which marketed nasal spray pumps that are capable of delivering an appropriate dose of a composition. (*See* DX38; DX12; DX39; DX40.)

2. Prior Art Aqueous Nasal Sprays.

113. By July 3, 1995, there were numerous nasal steroid products on the market that were FDA-approved to treat allergic rhinitis. These products included Nasacort Nasal Inhaler, Beconase AQ, Vancenase AQ, Flonase and Nasalide®, among many others. (SUF ¶¶ 89, 138-142, 157.)

114. Nasalide was introduced in 1981, 15 years before Aventis' patent application. It was a nasal spray employing a cosolvent to dissolve the steroid. It was approved for treating

allergic rhinitis and it contained a glucocorticosteroid (flunisolide), EDTA, and benzalkonium chloride for stabilizing the product and preventing microbial contamination. (SUF ¶¶ 97, 99, 129-132, 142; DX59; DX14.)

115. The aqueous suspensions, Beconase AQ, Vancenase AQ and Flonase, were also available before July 3, 1995 and contained all of the claimed inactive ingredients except for EDTA. (SUF ¶¶ 101-120, 133-136.)

3. Thixotropy.

116. Flonase, Beconase AQ and Vancenase AQ are all thixotropic. (Lochhead Tr. at 65:21-66:3, 294:18-23, 295:12-20.) Starting as early as 1987, all these products used suspending agents, like mixtures of MCC and sodium CMC, to provide thixotropic properties, which, as noted, are important to suspending the drug particles to ensure accurate dosing while, at the same time, allowing for easy dispersal through a spray system. (SUF ¶¶ 113-118, 121-128; DX21; DX22; DX60; DX13; DX278; DX10; DX11.)

117. In addition to suspending the drug particles, formulators in the early 1990s believed a more viscous nasal preparation may also result in compositions that adhered better to the nasal mucosa after being sprayed into the nasal cavity. (DX9; DX10; DX11; DX12.)

118. At the same time, formulators often preferred a lower viscosity for spraying the composition into the nasal cavity as a mist of small droplets (rather than a stream) that would reach all of the target areas inside the nasal cavity. (SUF ¶¶ 127-128; DX38; DX10; DX11; DX12; DX13.)

119. Prior art aqueous nasal sprays such as Beconase AQ, Vancenase AQ and Flonase had the thixotropic properties that allowed them to accomplish both of these goals – that is, a

higher resting viscosity for suspension and a lower shear viscosity for spraying. (SUF ¶¶ 121-128.)

C. The Prior Art Discloses Every Element Of The Asserted Patent Claims.

1. The Prior Art Discloses Every Element Of '573 Patent Claims 5, 6, 22, 35 And '329 Patent Claim 26.

120. The prior art products disclose nearly all of the elements of claim 5 of the '573 patent and, indeed, there is no dispute over most of those elements:

'573 Patent Claim 5	Prior Art
An aqueous pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual, which is odorless, propellant-free, and has a pH of about 4.5 to about 7.5, and which comprises:	Flonase, Beconase AQ and Vancenase AQ are propellant-free aqueous pharmaceutical compositions capable of being sprayed into the nasal cavity of an individual. (SUF ¶¶ 101-106; DX14; DX16; DX18; DX19.) Beconase AQ and Vancenase AQ have a pH between 4.5 and 7.0. (SUF ¶¶107-108; DX14; DX18; DX19; DX34.)
(A) at least about 85 wt. % of water;	
(B) about 0.001 to about 2 wt. % of solid particles of triamcinolone acetonide medicament;	Flonase, Beconase AO and Vancenase AQ contain a glucocorticosteroid. (SUF ¶¶ 109-110; DX14; DX16; DX18; DX19.) Nasacort Nasal Inhaler discloses the use of TAA at 55 mcg/spray. (SUF ¶ 139; DX15.)

(C) about 1 to about 5 wt. % of a suspending agent comprising a mixture of about 85 to 95 wt. % of microcrystalline cellulose and about 5 to about 15 wt. % of carboxymethyl cellulose based on the weight of the mixture, the amount of suspending agent being effective to maintain said solid particles dispersed uniformly in the composition and to impart to the composition the following thixotropic properties: (i) the viscosity of the composition in unsheared form is about 400 to about 800 cp; (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition is about 50 to about 200 cp and such that the composition in the form of a mist flows readily into the nasal passages for deposit on the mucosal surfaces of the nasal cavity; and (iii) in deposited form on the mucosal surfaces, the viscosity of the composition is about 400 to about 800 cp and such that it resists being cleared from the mucosal surfaces by the inherent mucocillary forces which are present in the nasal cavity; and	Flonase, Beconase AQ and Vancenase AQ contain a mixture of microcrystalline cellulose ("MCC") and carboxymethylcellulose ("CMC") sodium, (SUF ¶¶ 113-118; DX14; DX16; DX18; DX19.) This suspending agent will maintain the particles of drug dispersed uniformly in the compositions. (DX14; DX16; DX18; DX19; '573 patent col. 5:25-37.) Additionally, this suspending agent imparts thixotropic properties to each of the prior art compositions. (SUF ¶¶ 121-128; DX21; DX22; DX60; DX21; DX278; Lochhead Tr. at 65:21-66:3; Prud'homme Tr. at 7:3-4; DX23; DX29.)
(D) about 0.004 to about 0.02 wt. % of a quaternary ammonium compound that has anti-microbial properties; and	Flonase, Beconase AQ and Vancenase AQ contain benzalkonium chloride, which is a quaternary ammonium compound that has antimicrobial properties (SUF ¶¶ 119-120; DX14; DX16; DX18; DX19; DX44 at 27 (concentration of 0.002-0.02%).)
(E) about 0.01 to about 0.5 wt. % of a chelating agent.	The use of EDTA as a chelating agent to stabilize corticosteroids and in conjunction with benzalkonium chloride was disclosed and well known in the art in July 1995. (DX44.)

121. Aventis does not dispute that the prior art products contain nearly all of claim 5's elements. The only disputes are: (1) whether the prior art is odorless; (2) whether the prior art discloses EDTA; (3) whether the prior art exhibits the claimed thixotropic properties; and (4) whether the prior art discloses TAA in the claimed formulation.

a. The Prior Art Products Were "Odorless."

122. "Odorless," as construed by the Court based on the parties' stipulation, means "odors that cause the user discomfort are absent." (D.I. 114, '573 patent, p. 4.) Flonase,

Beconase AQ and Vancenase AQ are "odorless" as construed by the Court because none of them has an odor that cause users discomfort.

123. Flonase, Beconase AQ and Vancenase AQ contain phenylethyl alcohol, which has a rose scent. (DX62.) There is no evidence that this scent causes user discomfort.

124. Studies that Aventis conducted, including a study by Bachert, *et al.*, show that some but by no means all subjects simply *preferred* the odor of Nasacort AQ, not that it caused them "discomfort." Indeed, many subjects preferred the scent of compositions like Flonase that contain phenylethyl alcohol, which demonstrates that it did not cause them discomfort. (DX49.)

125. The study's own author, Dr. Bachert, has acknowledged that Flonase's odor was not necessarily considered "unpleasant" but simply "less preferred" by some patients. (DX91.)

126. Moreover, the Bachert study demonstrated no statistically significant difference in product comfort between Nasacort AQ and Flonase or Beconase AQ. (DX51; DX220; DX50; DX53; DX54.) Because they all produce the same level of user comfort as Nasacort AQ, prior art products Flonase, Beconase AQ and Vancenase AQ are all "odorless" within the meaning of claim 5 of the '573 patent.

127. Additionally, the patents list "phenyl ethyl alcohol" as an example of an acceptable antimicrobial agent for the claimed composition, despite making clear that ingredients that cause user discomfort must be avoided. ('573 patent, col. 6:17-24; col. 1:58-60.) If phenylethyl alcohol caused user discomfort due to its scent, it would not be an acceptable excipient. Thus, the patent makes clear that it is "odorless" within the meaning of the claims.

128. In any event, a person of skill in the art in July 1995 would know to use EDTA in place of phenylethyl alcohol if its scent truly caused user discomfort. Key formulation references, such as the Handbook of Pharmaceutical Excipients and Remington's Pharmaceutical

Sciences, disclosed before July 3, 1995 that EDTA was odorless and that phenylethyl alcohol had a rose scent. (DX44; DX62.)

129. Replacing phenylethyl alcohol with EDTA would therefore be a routine substitution to a formulator, just as it was to the Aventis marketing department during Nasacort AQ formulation. (DX133.)

b. The Prior Art Disclosed The Use Of EDTA In Nasal Preparations.

130. The use of a chelating agent, and specifically the use of EDTA in nasal formulations, was also well known to formulators by July 3, 1995. (SUF ¶¶ 92, 93, 129-130.)

131. Using EDTA was particularly routine in this context where every prior art formulation used "benzalkonium chloride" as a preservative. (SUF ¶¶ 119, 120, 129-132.) The Handbook explains that EDTA, within the claimed concentration ranges, has a "synergistic" effect in fighting a key microbe when paired with benzalkonium chloride. (*See* DX44; *see also* DX45; DX34; DX48; Lochhead Tr. at 293:15-21; SUF ¶¶ 129-132.) The Handbook also discloses that EDTA may be used as a chelating agent to stabilize corticosteroids through the typical functions of a chelating agent and in place of an antioxidant. (DX44; DX38.)

132. Moreover, many nasal products available before July 1995 contained a combination of EDTA and benzalkonium chloride, including: Afrin®, Duration®, Otrivin®, Privine®, Salinex®, Vicks Sinex®, Nasalide® and Nasalcrom®. (SUF ¶¶ 129-132; DX46; DX47; DX14; DX17; DX12; Meltzer Tr. at 139:12-17, 144:14-144:22.)

133. The claimed range of EDTA of 0.01 to 0.5 wt. % is disclosed in the prior art. (DX44; DX12.) And there is no evidence that it or the specific amount of 0.05 wt. % in Example 1 produces any unexpected results. Thus, arriving at the claimed range of 0.01 to 0.5 wt. % would be a matter of routine optimization.

c. The Prior Art Discloses The Claimed Thixotropic Properties.

134. There is no dispute that Flonase and Beconase AQ meet the claimed setting or unsheared viscosity of "about 400 to about 800 cp" or "about 400 to about 1000 cp" of '573 patent claim 5 and related claims. All of the experts agree. (Lochhead Tr. at 234:13-20; SUF ¶¶ 123, 124; DX318.)

135. The prior art also discloses the remainder of the claimed thixotropic properties.

i. Dr. Klingenberg's Testing Of Flonase Shows That It Exhibits The Claimed Shear Viscosity.

136. Dr. Daniel Klingenberg, a Barr expert, measured the viscosity of Flonase using the method described in the patent and concluded that it has unsheared and shear viscosities falling within the claimed ranges.

137. The method to be used in viscosity testing of the claimed composition is set forth briefly in the patent specification. ('573 patent, col. 5:18-24.) This description leaves open many ambiguities, including, for the shear viscosity measurements: which position on the Burrell wrist action shaker the sample is attached to, what container to use to shake the material, and how full that container must be when shaken – all of which can potentially impact the final results.

138. Dr. Klingenberg measured the viscosity of Flonase using the method described in the patent, after performing several experiments to resolve these ambiguities as well as others.

139. After his experimentation to determine the appropriate methods, Dr. Klingenberg conducted the testing and concluded that Flonase has a shear viscosity of 165 to 206 centipoise, within the claimed shear viscosity range. Dr. Klingenberg's methods were wholly consistent with the patent specification's sparse description as it would be understood by one of skill in the art. For instance, Aventis complains that Dr. Klingenberg poured the composition from the

container after using the wrist shaker before measuring viscosity thereby imparting additional shear to the product. But that is exactly what Aventis did with its own internal testing. (DX176 ("[a]fter 5 minutes on the shaker, remove the container. *Shake the container vigorously*, and then" measure the viscosity on the Brookfield viscometer.))

ii. Achieving The Claimed Viscosity Ranges Is A Matter Of Routine Optimization.

140. In any event, there is nothing surprising about the claimed thixotropic properties, nor is there anything novel about the claimed viscosity ranges.

141. In fact, the claims set forth an appropriate range for the ratio of MCC and CMC that specifically covers the commercially-available Avicel products. (SUF ¶¶ 174-177.) For instance,

(SUF ¶¶ 113-116; DX18; DX42.) Beconase AQ and Vancenase AQ contain mixtures of CMC and MCC

(SUF ¶¶ 113-114, 117-118.)

142. Additionally, Avicel CL-611 is within the claimed ranges of MCC and CMC for the suspending agent. (SUF ¶¶ 174-177; DX42.) A person of ordinary skill in the art would have been motivated to use either Avicel RC-591 or CL-611 in such a formulation. (DX34.)

143. Aventis has produced no evidence to show that the claimed viscosity ranges produce any surprising or unexpected results for this formulation.

144. Moreover, determining the appropriate viscosity characteristics for a nasal spray is a matter of routine optimization to ensure that the unsheared viscosity is high enough to suspend the active ingredient and that the shear viscosity is low enough to allow for dispersal through spraying. (DX38; DX24; SUF ¶¶ 121-128.) There is nothing "inventive" about such routine optimization, as Aventis' specification acknowledges:

> Suitable values for the setting viscosity and for the shear viscosity of the composition can be determined for a particular composition, taking into account also the particular means used to apply the composition to the nasal cavities.

('573 patent, col. 5:10-13.)

iii. In Deposited Form, Flonase, Beconase AQ and Vancenase AQ Would Behave The Same As Nasacort AQ Or Barr's ANDA Product.

145. The viscosities of Nasacort AQ, Flonase, Beconase AQ and Vancenase AQ when in the nasal cavity are unknown. (*See* Alcorn Tr. at 340:7-17; Kim Tr. at 116:23-117:8.) Nevertheless, Flonase, Beconase AQ and Vancenase AQ would behave similarly to Nasacort AQ in deposited form on the nasal mucosa.

146. All three products eventually return to their unsheared viscosities when allowed to sit outside the body in a container – that is, "*in vitro*." (DX23; DX29; DX301.) Therefore, if *in vitro* testing is enough to show that Nasacort AQ and Barr's ANDA product return to unsheared viscosity after being sprayed into the nasal cavity (which Barr denies), the same evidence demonstrates that Flonase, Beconase AQ and Vancenase AQ would return to their unsheared viscosity in deposited form as well. (DX301.)

iv. The Prior Art Deposits Pharmaceutically Effective Amounts Of Glucocorticosteroids On The Same Mucosal Surfaces Of The Nasal Cavity As Nasacort AQ.

147. In terms of the ability of the claimed compositions to reach the entire nasal cavity and "resist[] being cleared from the mucosal surfaces," the prior art formulations have the same exact ability as Nasacort AQ. (SUF ¶¶ 103-104, 127-128.)

148.

149. Because Beconase AQ and Vancenase AQ have similar formulations (DX18; DX19), they would be expected to perform the very same way. Therefore, the prior art meets these limitations to the same extent as Nasacort AQ.

d. The Prior Art Discloses The Use Of TAA In The Claimed Composition.

150. A person of ordinary skill in the art would reasonably expect that he or she could simply swap out the glucocorticosteroids in the prior art formulations (such as Flonase, Beconase AQ or Vancenase AQ) to create an aqueous nasal spray using TAA, such as the nasal spray described by Settipane and Kobayashi, the two references discussing Aventis' clinical trials on Nasacort AQ. (SUF ¶¶ 95-96, 99, 111-112, 168-169.)

151. Before July 1995, a powerful and undisputed motivation existed for making an aqueous nasal spray containing TAA, which was already FDA-approved to treat allergic rhinitis as Nasacort Nasal Inhaler at 55 mcg/spray, 220 mcg once daily. (SUF ¶¶ 89-91, 98, 139, 168-169; DX15.) That motivation was doubly powerful given the push to remove CFCs from nasal products and the patient preference for aqueous formulations over aerosols. (DX33; DX34.)

152. The similarity of chemical structures and relative solubilities of TAA, fluticasone propionate and beclomethasone dipropionate would also inform skilled artisans that these different steroids could be substituted for one another in the same formulation. (SUF ¶ 99; DX41; DX353; DX14; DX16.)

153. The patent specification further confirms the substitutability of these steroids by noting that the claimed composition could be used with many steroids, including "clomethasone, dexamethasone, fluticasone, prednisolone and triamcinolone acetonide." ('573 patent, col. 4:1-9.) Indeed, Dr. Kim, the named inventor (SUF ¶ 10), obtained a similar patent claiming the same

formulation as '573 patent claim 5 with at least two other steroids mentioned in the '573 and '329 patents. (DX61.)

154. Settipane and Kobayashi disclose an aqueous TAA nasal spray at a pharmaceutically effective dose of 55 mcg/spray, 220 mcg administered once daily. (SUF ¶¶ 168-169.) A skilled artisan would be able to use that disclosure, coupled with the excipients from other FDA approved aqueous glucocorticosteroid nasal sprays, to formulate an aqueous TAA nasal spray.

155. The fact that a skilled artisan could make a water-based form of CFC-based Nasacort was also readily apparent from the successful switch in 1987 from CFC-based Beconase to water-based Beconase AQ and Vancenase AQ.

2. The Prior Art Discloses Every Element Of '329 Patent Claim 13 And '573 Patent Claims 7, 8, 23-24, 27-28.

156. None of the other claims adds anything that is allegedly novel or unobvious. Claim 13 of the '329 patent, for instance, contains many of the same requirements in '573 patent claim 5, including a thixotropic aqueous composition containing TAA, a mixture of MCC and CMC, EDTA, benzalkonium chloride, and purified water. (*See supra*, ¶ 120.)

157. Flonase, Beconase AQ and Vancenase AQ all have relatively high unsheared viscosities and relatively low shear viscosities, and would behave the same in deposited form as would Nasacort AQ and Barr's ANDA product. Thus, they are all thixotropic. (*See supra* ¶¶ 134-149; SUF ¶¶ 121-128; Lochhead Tr. at 295:12-20; Prud'homme Tr. at 7:3-4.)

158. Claim 13 also adds limitations for an article of manufacture that includes the composition, a vessel and a precompression pump, as well as the routine use of dextrose and polysorbate 80. Similarly, '573 patent claims 7, 8, 23-24 and 27-28 require a dispersing agent, including polysorbate 80, in an amount of about 0.001 to about 0.01 wt.%.

159. Flonase, Beconase AQ and Vancenase AQ used similar pumps with associated vessels to contain the composition. (*See* SUF ¶¶ 143-147; DX14; DX16.)

160. Moreover, Valois and Pfeiffer pumps were commercially available before July 3, 1995. Both were equally capable of reproducibly delivering a full dose of composition to the nasal cavity. Precompression pumps such as the Valois VP7 were sold before July 1995 and used for nasal preparations. (*See, e.g.*, DX12; DX38; DX39; DX40.) The precompression pump and vessel were well known to a person of ordinary skill in the art in 1995.

161. The addition of dextrose and polysorbate 80 in a range of about 0.001 to about 0.01 wt. % were also disclosed in the prior art. Flonase, Beconase AQ and Vancenase AQ contain dextrose as well as polysorbate 80 .

(SUF ¶¶ 133-136; DX18; DX19.)

162. Thus, the prior art discloses each element of '329 patent claim 13 and '573 patent claims 7, 8, 23-24, 27-28.

3. The Prior Art Discloses Every Element Of '573 Patent Claims 21 And 34 And '329 Patent Claims 14 And 25.

163. '573 patent claims 21 and 34 and '329 patent claims 14 and 25 claim methods of treating allergic rhinitis with an aqueous thixotropic composition, methods of applying solid particles of TAA to the nasal mucosa and methods of applying an aqueous pharmaceutical composition containing pharmaceutically effective amounts of TAA to the nasal mucosa.

164. With the exception of a different active ingredient, Flonase, Beconase AQ and Vancenase AQ all meet these method claim requirements. (*See* DX14; DX16; SUF ¶¶ 127-128, 138, 140-142; *supra* ¶ 120.) Moreover, they each contain an amount of glucocorticosteroid that is effective in treating allergic rhinitis by virtue of being present on the nasal mucosa. (SUF ¶¶ 95-96, 99, 113-118; DX14; DX16.)

165. Additionally, Flonase, Beconase AQ and Vancenase AQ contain a suspending agent that imparts thixotropic properties to the composition. (*See supra*, ¶¶ 120, 134-149; SUF ¶¶ 113-118.)

166. And the glucocorticosteroids in each of these prior art compositions would deposit and remain on the same mucosal surfaces as Nasacort AQ. (*See supra* ¶¶ 147-149.)

167. Thus, the prior art discloses every element of claims 21 and 34 of the '573 patent and claims 14 and 25 of the '329 patent.

4. The Prior Art Discloses Every Element Of Claim 26 of '573 patent, And Claims 15-16, 23-24 Of The '329 Patent.

168. '573 patent claim 26 and '329 patent claims 15-16 and 23-34 add requirements of (1) once daily dosing; (2) spraying a full dose of 55 mcg of triaminolone acetonide into a nostril; (3) spraying two full 55 mcg/spray doses into a nostril once daily; and (4) spraying a total of 100 to 130 mcg into a nostril daily. Each of these requirements is disclosed by Flonase, Nasacort Nasal Inhaler, and Settipane and Kobayashi.

169. Nasacort Nasal Inhaler was FDA approved to treat allergic rhinitis through the claimed dosing regimen. (SUF ¶ 139; DX15; DX64.)

170. Given the proven safety and efficacy of Nasacort Nasal Inhaler at that dose, a person of ordinary skill in the art would have reasonably expected the same dosing regimen would work for an aqueous formulation, particularly in view of the Settipane and Kobayashi disclosures of an aqueous TAA formulation with the same dosing regimen. (SUF ¶¶ 139, 168, 169; DX34; DX35; *supra* ¶¶ 150-155; *see also* DX16 (similar dosing for Flonase).)

171. Thus, the claimed dosing regimens in '573 patent claim 26 and '329 patent claims 15-16 and 23-24 were disclosed by the prior art.

5. Additional Prior Art Further Demonstrates That The Asserted Claims Are Obvious.

172. Other prior art demonstrates that Aventis' patents claim an exceedingly basic and routine formulation for nasal sprays. For instance, PCT Application No. WO 92/14473 ("the '473 application") is directed to an aqueous nasal spray suspension containing a steroid called tipredane. (SUF ¶¶ 200, 201.)

173. The '473 application, which discusses the motivation to avoid CFC-propelled nasal sprays, describes an aqueous nasal spray containing a steroid used to treat allergic rhinitis and "a pseudoplastic thixotropic viscosity modifying agent," including Avicel RC-591. (DX13.) The patent discloses using that agent in the same range as Aventis' patents while explaining the formulation's viscosity will be relatively low to spray the composition and relatively high for storage. (DX13.)

174. The '473 application also describes the following characteristics in common with the asserted claims of the '573 and '329 patents: an ionic or nonionic surfactant; a preservative such as benzalkonium chloride; a tonicity adjusting agent; a pH between 4.5 and 7.5; and once daily dosing. (DX13.)

175. PCT Application No. WO 92/04365 ("the '365 application") is directed to pharmaceutical formulations of mometasone furoate, the active ingredient in Nasonex, which was a nasal steroid spray introduced shortly after Nasacort AQ. The '365 application describes an aqueous nasal spray containing mometasone furoate to treat allergic rhinitis that includes suspending agents, including Avicel RC-591; pH-adjusting agents; polysorbate 80; benzalkonium chloride; isotonicity adjusting agents; and water. (DX43; SUF ¶¶ 174, 200-201.)

176. PCT Application No. WO 94/05330 ("the '330 application") describes an aqueous nasal spray with a Valois VP7 pump. (DX12.) The '330 application further describes the

disclosed composition as having a low shear viscosity that is relatively high and a high shear viscosity that is relatively low. This makes the composition sprayable in low viscosity form and "upon contact with the mucosal linings of the nasal cavity the viscosity of the composition increases to form a gel" which "minimizes the common problem of roll-back . . . where the liquid runs down the back of the throat or out of the front of the nose." (DX12.) The '330 application also discloses other ingredients like anti-inflammatory agents and anti-allergic agents; surfactants; preservatives including benzalkonium chloride; and EDTA. (DX12; SUF ¶¶ 200-201.)

XIV. Secondary Considerations Of Non-Obviousness.

177. Aventis has asserted several secondary considerations of non-obviousness that, it contends, rebut Barr's prima facie obviousness case. But neither alone nor together do these alleged secondary considerations rebut the prima facie case of nonobviousness.

A. Aventis Cannot Demonstrate Any Unexpected Results From Nasacort AQ.

1. Relative Steroid Potency Does Not Demonstrate Unexpected Results.

178. Aventis has failed to show any surprising results. Aventis claims to have produced unexpected results in the claimed dosing regimen to be clinically effective. To the contrary, it is exactly what one would have expected.

179. Studies comparing the efficacy of Nasacort AQ to other intranasal corticosteroid sprays have found no significant difference in clinical efficacy. (PTX 408; DX85; DX332; DX330; Meltzer Tr. at 187:10-17; *see also* Meltzer Tr. at 192:15-193:13 (steroid's performance in nasal cavity does not depend on potency alone and, instead, also depends on other factors); *accord* PTX 391; Mackay Tr. at 200:15-18, 202:7-204:10; PTX 662; Meltzer Tr. at 206:3-21.)

180. Moreover, it was well-known that TAA had sufficient potency to be efficacious at the claimed once daily dose and, thus, it is hardly surprising that TAA works effectively. (DX15; DX10; DX11; *supra* ¶¶ 150-151, 154.)

2. Nasacort AQ Does Not Demonstrate Any Statistically Significant Differences From Flonase In Nasal Deposition Or Clearance.

181. As explained above,

182. Despite these similarities, Aventis apparently seeks an inference that Nasacort AQ exhibits a difference in deposition pattern that makes it an unexpected improvement over Flonase.

183. In a responsive expert report,

184. Dr. Berridge's analysis did not yield accurate numbers. Moreover, he failed to use a basic correction, such as a Bonferroni correction, that is mandatory for multiple comparisons such as the ones Dr. Berridge attempted to make.

3. Nasacort AQ Does Not Demonstrate Improved Stability Over Prior Art Products.

185. Dr. Lochhead initially asserted in his expert report that an unexpected benefit of the claimed invention is that a supposedly "narrow" 200 centipoise difference between the

setting and shear viscosity could provide a product that exhibits long-term stability at rest, and desirable sprayability characteristics in sheared form. (DX318.)

186. But Dr. Lochhead gave up on this argument at his deposition, conceding the lack of any unexpected results when considering the full scope of the claims also covering a broader 750 centipoise difference (from 50 centipoise sheared to 800 centipoise unsheared). (Lochhead Tr. at 298:1-5, 300:8-23, 302:24-303:6.)

187. Dr. Lochhead's own viscosity testing shows the difference between the unsheared and shear viscosity of Nasacort AQ is no less than 337 centipoise (not 200 centipoise), and could be as much as 375 centipoise. (DX318.)

4. Improvement In Eye Symptoms By Nasacort AQ Was Not Unexpected.

188. Aventis, relying on Settipane (DX10), asserted at one point that Nasacort AQ provided "an unexpected benefit in terms of the treatment of eye symptoms." (DX316 at ¶ 83.) Because Settipane is prior art and disclosed this property of TAA before July 3, 1995, there was nothing unexpected about that property as of July 3, 1995.

189. Moreover, Aventis' expert, Dr. Kaliner, conceded during his deposition that a number of intranasal preparations have been reported to improve eye symptoms, including Flonase. (Kaliner Tr. at 365:9-366:20, 368:20-369:13, 386:12-387:19; DX92; DX331.)

B. Aventis Has Failed To Prove A Long-Felt, Unmet Need For The Claimed Invention.

190. Aventis has failed to produce any evidence or any expert testimony of any purported long-felt, unmet need that only the claimed invention met. Indeed, the pharmaceutical industry was in the midst of rapidly producing aqueous-based sprays to replace CFC-propelled

sprays. Many were safe and effective in treating adults and children, including for once daily dosing.

191. Moreover, there is no evidence that the odor of other intranasal steroid sprays caused patients to "need" a replacement nasal spray. The difference between Nasacort and rose-scented nasal sprays is a matter of simple consumer preference driven by marketing concerns, not a patentable invention. Indeed, studies comparing patient preference for intranasal steroid sprays have shown that the treatments are "well-tolerated"; "equally comfortable to take"; and have no statistically significant difference in overall comfort. (PTX408; DX51; DX50.)

192. Notably, the odor of Beconase AQ has been reported to be well below the level of "slightly bothersome." (PTX408.) Similarly, in a five-year study of patients who had undergone endoscopic sinus surgery and were taking Flonase, no patient stopped using the medication because the taste or smell was unacceptable. (DX89.)

193. To the extent that any study showed a preference for Nasacort AQ, odor was only one of several attributes impacting that preference. (DX91.)

Indeed, a study has shown that, when asked whether Nasacort AQ, Flonase, or Nasonex was "most preferred to be prescribed," over half of the subjects did not designate Nasacort AQ as "most preferred." (PTX394.)

194. Although one study reported that Nasacort AQ was "more comfortable" than Flonase and Nasonex, the study reported no significant difference with respect to "like/dislike odour." (PTX394.) Due to the design of the studies, including suggestive wording, no conclusion can be drawn as to whether there was a preference for Nasacort AQ based on odor. (DX90; Meltzer Tr. at 234:12-19; *accord* PTX408; DX51; DX50; PTX394.) Nor is there any

evidence that any purported patient preference for Nasacort impacted patient compliance. (Mackay Tr. at 323:23-24, 376:1-4; 376:13-16, 381:10-11; PTX394; Meltzer Tr. at 253:4-8, 282:7, 296:15-21, 310:22, 311:1.)

195. Thus, there is no evidence of a long-felt, unmet need for the claimed invention.

C. Aventis Has No Evidence That Others Tried, But Failed To Make The Claimed Invention.

196. Aventis also has failed to show that anyone failed to make the claimed formulation, including the formulators of Tri-Nasal Spray.

197. Tri-Nasal Spray was an aqueous intranasal spray with TAA as its active ingredient. Unlike Nasacort AQ, Tri-Nasal Spray employed a co-solvent system containing propylene glycol and polyethylene glycol, which can cause nasal burning and stinging. Therefore, Tri-Nasal Spray does not fall within the scope of the claims of the '573 and '329 patents. (PTX 398; Meltzer Tr. at 172:24-173:7, 177:5-16.)

198. Tri-Nasal Spray experienced a number of problems, including instability and precipitation at cold temperatures, and was ultimately recalled due to leaking containers. This shows nothing more than a failure of the Tri-Nasal Spray formulators to use an acceptable manufacturing process and containers. It does not demonstrate that they tried but failed to make the claimed invention or solve the problem it purports to solve. (Meltzer Tr. at 180:17-181:6.)

D. Aventis Cannot Prove That Other Brand Products Copied Nasacort AQ.

199. Aventis asserts, without any evidence whatsoever, that other brand products, Tri-Nasal Spray, Nasonex and Veramyst, copied the patented invention simply because they do not contain phenyl ethyl alcohol or do contain EDTA.

200. But there is no evidence that formulators of Tri-Nasal Spray had any intention of copying Nasacort AQ with respect to the use of EDTA. (Meltzer Tr. at 176:10-20.) A more

reasonable inference is that the Tri-Nasal Spray formulators were copying other cosolvent systems like Nasalide and Nasarel, both of which contain EDTA. (DX14; DX17.)

201. Moreover, Aventis offers no evidence that the formulators of Veramyst or Nasonex had any intention of copying the claimed invention. (Meltzer Tr. at 326:3-327:2.) Veramyst may contain EDTA, for instance, due to stability differences between the fluticasone furoate and fluticasone propionate molecules. Nasonex may have removed phenylethyl alcohol due to its interactions with the active molecule or glycerin, neither of which is in Nasacort AQ.

E. Aventis Cannot Prove Commercial Success.

1. Nasacort AQ Is Not A Commercial Success.

202. Aventis offers no evidence of commercial success, which is difficult in the pharmaceutical industry given the high capital (estimated at $800 million to $1.7 billion), and correspondingly high risk, involved in the development and commercialization of such products, which involves the arduous FDA process. (DX 94; DX 95; Bell Tr. at 59; Kaliner Tr. at 172:18-181:3; Zak Tr. at 260:17-261:1.)

203. Far from being a commercial success based on the attributes of the claimed invention – an allegedly favorable thixotropic profile and absence of odor – Aventis offers no convincing evidence that Nasacort AQ was even profitable for *any* reason, much less tying that commercial success to the claimed "innovative" attributes. (DX312; Zak Tr. at 263:13-263:23.)

(DX102.)

204. The IMS data upon which Aventis relies is not actual net sales, but only an estimate based on the average wholesale price which can be as much as 20% higher than actual dollars. (Bell Tr. at 205:20-208:5; Zak Tr. at 176:6-178:17; DX137; DX138; DX139; DX Demo. 11, 12.)

205. If IMS data is considered, Nasacort AQ's performance pales in comparison to that of its two key competitors – Flonase and Nasonex – even when it is combined with the Nasacort Nasal Inhaler. (Zak Tr. at 83:16-85:5; DX Demo. 7, 8, 9, 13 & 14; Bell Tr. at 222:11-224:18; DX102.) Flonase drove INS market expansion, and both Flonase and Nasonex outperformed Nasacort AQ prescriptions at a rate of 2 to 1, or more. (DX312; DX Demo. 7, 13, 14; *see also* Kaliner Tr. at 135:9-135:13; Mackay Tr. at 358:7-358:13.) While Flonase and Nasonex each ranked as the third nasal spray in the first full year after they launched, Nasacort AQ ranked only seventh the first full first year after it launched. (Bell Tr. at 222:11-224:18.)

206.

Nasacort AQ was never the number one, or even number two, INS product in either sales or prescriptions. (Zak Tr. at 157:2-158:13; DX Demo. 13.)

207.

Nasacort AQ's market share growth was much slower than even that of the Nasacort Nasal Inhaler, and, in fact, Nasacort AQ never reached the peak share achieved by the Nasacort Nasal Inhaler. (DX Demo. 8.)

208.

209.

Nasacort AQ was less expensive than Flonase and Nasonex from 1996-2001. (DX312 at 4.3) When Aventis increased the price of Nasacort AQ in 2002, there was a corresponding increase in revenues. (Bell Tr. at 289:17-289:24.)

2. Aventis Did Not Show The Requisite Nexus Between Its Purported Commercial Success And The Patented Features Of The Invention.

a. Aventis Failed To Show That Any Sales Were Specifically Due To The Purported Patented Features Of Nasacort AQ.

210. As noted, there is no evidence tying any increase in Nasacort AQ sales to the purported patented features, thixotropic formulation and odorlessness.[3] There is no evidence from consumers that they preferred Nasacort AQ to Flonase or Nasonex on the basis of either purported feature.

211. Physicians deem nasal spray products as essentially the same. (DX 334; DX115; DX110; Kaliner Tr. at 135:1-135:5; Mackay Tr. at 184:2-185:14; Bell Tr. at 263:4-265:5.)

(Bell Tr. at 282:20-284:16; DX129; DX130; Zak Tr. at 102:4-102:10, 161:8-161:15.)

212. Pharmaceutical companies use marketing to differentiate such products, and Aventis similarly relied on marketing messages for the purpose of increasing Nasacort AQ sales. (Zak Tr. at 111:15-112:5.) Physicians rely on pharmaceutical product promotion for much of their information about the products. (Bell Tr. at 183:17-186:4.)

[3] Aventis' expert attempts to include additional features such as comfort, lack of taste, and "general efficacy." DX312 at ¶ 25. None of these are patented features and, therefore, cannot form the basis for a commercial success nexus.

213. Here,

(DX312; Zak Tr. at 102:11-103:16.) The broad and varied messages included: "first-line therapy for rhinitis"; "Nasacomfort"; "choice" between a wet or dry formulation of TAA; "odorless" and "taste-free"; "Stays Where It's Sprayed"; and "patient-preferred." (DX13; DX108; DX110; DX113; DX116; DX120; DX125.)

214. And (Zak Tr. at 118:7-118:13; Bell Tr. at 181:12-181:20, 183:1-183:8, 242:7-244:17, 247:22-248:5, 256:5-256:20; DX111; DX312.)

215.

b. Nasacort AQ Sales Were Based On Factors Other Than The Purported Patented Attributes.

216. One reason for Nasacort AQ sales was the steroid, TAA, which was used in the Nasacort Nasal Inhaler since 1991 and had an established profile with physicians. (Kaliner Tr. at 239:10-239:16, 241:4-241:14; DX105; DX106; DX107.)

217. Aventis has pursued a steroid-based, "choice" message for the Nasacort franchise from the outset, (DX124; DX110),

218. With Aventis' encouragement, Nasacort Nasal Inhaler patients were switched to Nasacort AQ in anticipation of, and after, the Inhaler's removal from the market. (DX120;

DX136; DX246; DX324; DX329; DX325; DX333; DX247; DX98; DX326; DX327; DX328; Zak Tr. at 125:11-125:16, 127:22-128:3; Bell Tr. at 235:1-238:9.)

219. It is reasonable to infer that some physicians and patients remained with TAA rather than begin a new corticosteroid. Indeed, as Nasacort AQ's market share increased, Nasacort Nasal Inhaler's share declined. (DX Demo. 8.)

220. Nasacort AQ's sales also resulted from substantial promotion.

(DX102; DX Demo. 12.)

(DX312 at 3.1; Bell Tr. at 210:18-211:5; *accord* DX298 at 29).

221. Nasacort AQ may also have benefited from Aventis' promotion of Nasacort Nasal Inhaler. The two products shared the Nasacort name, the same steroid.

(Bell Tr. at 327-28; DX102; DX335; DX352; Bell Tr. at 165:1-3; Zak Tr. at 145:2-10; SUF ¶ 139.)

CONCLUSIONS OF LAW

222. Barr is entitled to a judgment of noninfringement and patent invalidity for the reasons detailed below and highlighted in the introduction to this brief. In summary, Barr's ANDA product does not infringe any of the asserted claims for multiple reasons and Aventis patents are invalid for obviousness under Section 103, lack of enablement under Section 112, and anticipation due to prior public use under Section 102.

I. Barr's ANDA Product Does Not Infringe Any Asserted Claims.

223. Aventis bears the burden of proving by a preponderance of the evidence that Barr's ANDA product infringes the asserted claims of the patents-in-suit. *Centricut, LLC v. The Esab Group, Inc.*, 390 F.3d 1361, 1367 (Fed. Cir. 2004). It cannot meet that burden.

224. The determination of patent infringement involves a two-step analysis. "The court must first interpret the claims to determine their scope and meaning. It must then compare the properly construed claims to the allegedly infringing device." *PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1357 (Fed. Cir. 2004) (internal citation omitted). To prove patent infringement, "the patentee must show that the accused device meets each claim limitation, either literally or under the doctrine of equivalents." *Id.*

225. Under the Court's construction, Aventis must show that Barr's ANDA product meets at least the following elements: (1) in deposited form, the composition returns to its unsheared viscosity or a viscosity of about 400 to about 800 or 1000 centipoise; (2) the composition resists mucociliary clearance or retains TAA on the nasal mucosa; and (3) the composition deposits on the frontal sinus. (*See* Proposed Findings of Fact ("FOF"), ¶¶ 50-59)

A. Barr's ANDA Product Does Not Meet The Claim Requirement That It Return To A Specific Viscosity In Deposited Form On The Nasal Mucosa.

226. Aventis has no evidence that Barr's ANDA product either returns to its unsheared viscosity or returns to a viscosity within the range of about 400 to about 800 or 1000 centipoises when deposited on the mucosal surfaces of the nasal cavity.

227. The viscosity of Barr's ANDA product in deposited form on the nasal mucosa has never been measured, nor is there any known way to perform such an *in vivo* measurement; these facts are undisputed. (FOF ¶ 61.)

228. Therefore, Aventis relies solely on *in vitro* viscosity testing: first, viscosity testing its expert, Dr. Lochhead, performed on Barr's ANDA product during this litigation and, second, viscosity testing of Nasacort AQ with an inference that Barr's proposed ANDA product would behave in the same manner as Nasacort AQ. (FOF ¶ 61; DX321; Prud'homme Tr. at 178:3-10, 184:1-10.)

229. But the Federal Circuit has held that *in vitro* testing of an accused generic drug product is insufficient to prove infringement of a claim requiring *in vivo* effects, absent some evidence that the *in vitro* testing is a good model of *in vivo* behavior. *See Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1295-97 (Fed. Cir. 2006) (rejecting indirect evidence that *in vitro* dissolution rates with plasma concentrations could be used to show rate of *in vivo* dissolution and concluding: "Alza's evidence of *in vitro* dissolution rates is irrelevant absent evidence demonstrating that the *in vitro* system is a good model of actual *in vivo* behavior.").

230. This case is no different from *Alza*. Aventis has no direct evidence of the viscosity of Barr's ANDA product *in vivo*. The only *in vivo* evidence presented in this case is ; which establish nothing about the actual composition's viscosity in the nasal cavity. (*See* FOF ¶¶ 71-74; DX318.)

231. Aventis also has offered no expert testimony demonstrating that the *in vitro* viscosity testing "is a good model of actual *in vivo* behavior." *Alza*, 464 F.3d at 1297. In fact, the uncontroverted evidence in this case shows that *in vitro* viscosity testing is *not* a good model for *in vivo* behavior. The mucosal surfaces of the nasal cavity are substantially different than the environment in a Griffin beaker sitting in a 20°C laboratory. The nasal cavity is much warmer and, unlike a Griffin beaker, is constantly subjected to watery secretions, ciliary activity, and air flow. Any one of these things, by itself, can have an effect on the composition's viscosity.

Moreover, the composition is likely to be cleared from the nasal passages long before it returns to unsheared viscosity. (FOF ¶¶ 60-67.)

232. None of Aventis' experts has knowledge of both the environment of the nasal cavity and the effects that such an environment would have on the excipients in the claimed compositions. (*See* Kaliner Tr. at 254:10-15; Lochhead Tr. at 107:14-108:1, 112:5-11; Prud'homme Tr. at 104:24-105:6, 189:24-190:18.) Therefore, Aventis has not and cannot overcome the reality that its *in vitro* viscosity testing is an inadequate model of *in vivo* behavior. *See Alza*, 464 F.3d at 1295-97; *Centricut*, 390 F.3d at 1368 (holding that patentee's theory of infringement was insufficient where accused infringer presented expert testimony that theory might be untrue); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 972-73 (Fed. Cir. 2006) (holding that conclusory assertions of infringement are insufficient in the face of unrebutted expert testimony to the contrary). Aventis cannot prove infringement.

B. The Composition of Barr's ANDA Product Does Not Meet The Requirements That It Resist Mucociliary Clearance Or Retain TAA On The Nasal Mucosa.

233. Each of the asserted patent claims also requires the composition of Barr's ANDA product to "resist[] being cleared from the mucosal surfaces by the inherent mucociliary forces that are present in the nasal cavity" or to retain the TAA on the nasal mucosa. (*See* FOF ¶¶ 50-59.) Aventis has produced no evidence to show either.

234. Again, Aventis relies on nothing more than unproven theories. The only *in vivo* evidence on the behavior of Barr's ANDA product in the nasal mucosa are

(Berridge 8/3/07 Tr. at 41:5-42:23; Berridge 2/21/08 Tr. at 115:5-116:18; FOF ¶¶ 68-74.)

235. Aventis apparently seeks an inference that the composition resists clearance or retains TAA on the nasal mucosa .

(Berridge 2/21/08 Tr. at 120:23-121:7.) This inference is unwarranted. Dr. Berridge himself disavowed any expertise in nasal clearance and the inference he drew was unwarranted because the studies he relied on were not conducted on TAA particles, nor were they conducted with similar formulations to the claimed ones. (*Id.*)

236. In deposited form on the nasal mucosa, the formulation components of Barr's ANDA product could be rapidly diluted and cleared quickly while the TAA particles remain adherent to the epithelial surface of the nasal mucosa. (FOF ¶ 70.) Again, Aventis has no expert to testify to the contrary. (*See supra* ¶ 232.) Thus, Barr's evidence is uncontroverted.

237. Therefore, without any supporting evidence, Aventis' infringement claims fail. *See Centricut*, 390 F.3d at 1368; *Kao*, 441 F.3d at 972-73; *cf. Alza*, 464 F.3d at 1295-97.

C. Barr's ANDA Product Does Not Meet The Claim Limitations That It Deposit Or Remain On The Frontal Sinus For At Least About An Hour.

238. Every asserted claim requires Barr's ANDA product to deposit on the frontal sinuses. Several claims require it also to remain there for at least about an hour. (*See* FOF ¶¶ 50-59.) Barr's ANDA product will do neither and therefore, will not directly infringe any of the asserted claims. Moreover, this means that Barr cannot be liable for induced or contributory infringement of the method claims.

1. Barr's ANDA Product Will Not Deposit Or Remain On The Frontal Sinus For At Least About An Hour.

239. Barr's ANDA product will not deposit on the frontal sinus. Not only is it virtually impossible for a nasal spray to do so, but

(FOF ¶¶ 75-100.)

240.

The outlier study, the 1996 pilot study,

had a design anomaly, the cubic regions of interest, that make the frontal sinus results inherently unreliable. (FOF ¶¶ 75-100.)

241. In sum, Aventis has no competent evidence that Barr's ANDA product will deposit on the frontal sinus in any patient taking the product. Accordingly, Barr's ANDA product will not directly infringe any of the asserted claims.

2. Barr's ANDA Product Does Not Indirectly Infringe The Method Claims Under 35 U.S.C. § 271(b) Or (c).

242. Aventis also cannot prove that Barr would induce or contributorily infringe the method claims under 35 U.S.C. § 271(b) or (c).

243. Section 271(c) prohibits the sale of a product that can be used in a patented method if the product is "not a staple article or commodity of commerce suitable for substantial noninfringing use." Contributory infringement requires proof of direct infringement and also requires that the accused product have "*no use* except through practice of the patented method." *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1374 (Fed. Cir. 2003) (emphasis added)

(quotations omitted); *accord Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417, 441 (1984) (same).

244. Section 271(b) provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." Like contributory infringement, the burden of proving induced infringement is heavy: "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Acco Brands, Inc. v. ABA Locks Mfr. Co., Ltd.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (quotations and citation omitted); *see also Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990).

245. As discussed, Aventis cannot prove that Barr's ANDA product would directly infringe the asserted patent claims. This, by itself, is sufficient to defeat any indirect infringement claims. *See Acco*, 501 F.3d at 1312 (reversing verdict of induced infringement because of lack of evidence of direct infringement); *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1277 (Fed. Cir. 2004) (failure to prove direct infringement "dooms . . . allegations of indirect infringement").

246. Moreover, Barr's ANDA product is, without question, capable of substantial noninfringing use. Even Dr. Berridge concedes this. (Berridge 2/21/08 Tr. at 184:10-13.)

Therefore, Barr's ANDA product is capable of substantial noninfringing use and Barr cannot be liable for contributory infringement. *See Alloc*, 342 F.3d at 1374 (holding that flooring products could be installed by

methods not claimed in the patents and therefore had substantial noninfringing uses); *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 674 (Fed. Cir. 1990) (holding that jury could find substantial noninfringing use even if only 40% of uses are noninfringing).

247. These substantial noninfringing uses of the Barr ANDA product also defeat any inducement claims: "[T]he mere sale, without more, of a device capable of such non-infringing use will not establish liability for inducement." *Dynacore*, 363 F.3d at 1276. "Especially where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

248. Therefore, Aventis can prove neither contributory infringement nor infringement by inducement. *Dynacore*, 363 F.3d at 1277 (holding that defendants were not liable for contributory or induced infringement because of substantial noninfringing use); *Warner-Lambert*, 316 F.3d at 1365 (affirming judgment of noninfringement on contributory and inducement claims).

II. Aventis' Patents Are Invalid For Obviousness, Lack Of Enablement, And Anticipation.

249. The patents-in-suit are invalid for three, independent reasons: (1) obviousness under Section 103; (2) lack of enablement under Section 112; and (3) anticipation for prior public use under Section 102. Proving invalidity requires clear and convincing evidence. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60 (Fed. Cir. 2007). Barr has provided such evidence and, thus, Barr is entitled to a judgment of patent invalidity.

A. Aventis' Patents Are Invalid As Obvious.

250. Aventis' patents are directed to nothing more than a completely standard formulation for a nasal spray. It would have been exceedingly obvious in July 1995 for a skilled

artisan to formulate a thixotropic nasal spray for TAA – already FDA approved in a CFC-based aerosol – by combining TAA with the aqueous formulation ingredients of Beconase AQ, Vancenase AQ and Flonase. Routine substitution of ingredients from prior art formulations is simply not a patentable invention; instead, it is glaringly obvious under 35 U.S.C. § 103.

1. The Legal Standards For Obviousness Changed Under *KSR*.

251. 35 U.S.C. § 103(a) prohibits issuance of a patent if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious" to a person of ordinary skill in the art at the time of the patent application. In determining whether patent claims are obvious, the Court should consider: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; and (3) the differences between the prior art and the asserted patent claims. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

252. Secondary considerations of nonobviousness may be considered "to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.* at 17-18. But even when supported by substantial evidence, secondary considerations are often insufficient to overcome a prima facie case of obviousness. *KSR*, 127 S. Ct. at 1745-46 ("Where, as here, the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate."); *see also Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (affirming this Court's finding of obviousness based on the strong prima facie obviousness showing despite "substantial evidence" of secondary considerations).

253. Recently, as noted above, the Supreme Court in *KSR* changed the legal landscape of obviousness, holding that obviousness is judged under "an expansive and flexible approach" driven by "common sense," and thus, patentability requires "more than the predictable use of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1739.

254. Obviousness is now particularly appropriate in cases like this one involving patents directed toward a combination of previously known elements. The Court in *KSR* held: "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR*, 127 S. Ct. at 1740.

255. The Court further concluded that a patent claim can be proved obvious merely by showing that the combination of elements was obvious to try:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'. *When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.* If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. at 1742 (emphasis added).

256. The Court's new standard rejected the rigid application of the prior teaching, suggestion and motivation test employed by the Federal Circuit in favor of a more flexible obviousness standard. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 1741. Other forces, such as market demand, also may be examined to determine whether it would be obvious to combine more than one known element. *Id.* at 1741-42.

257. Because of this significant change in the legal landscape, the presumption of patent validity is entitled to even less weight here. The PTO considered these patent applications long before *KSR* and under a significantly different standard than that set forth by the Supreme Court in *KSR*. *Id.* at 1745 ("[T]he rationale underlying the presumption – that the PTO, in its expertise, as approved the claim – seems much diminished here."); *see also Ex Parte Kubin*, No. 07-0819, 2007 WL 2070495, at *5 (B.P.A.I. May 31, 2007) ("'[O]bvious to try' may be an appropriate test in more situations than we previously contemplated."). Therefore, *KSR* represents a significant reformulation of the obviousness standard – a standard not applied when the patent examiner allowed the patent claims in 1999.

2. A Person Of Ordinary Skill In The Art Is A Pharmaceutical Formulator Of Nasal Dosage Forms.

258. As detailed above, a person of ordinary skill in the art for these patents should have education and experience in pharmaceutical formulation of nasal dosage forms. *See Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007) (examining inventor's background, patent specification and problem invention tried to solve to determine that art was creation of compound to treat ear infections without damaging patient's hearing).[4]

259. Aventis apparently concedes that the level of ordinary skill includes pharmaceutical formulation, but ignores that the specification is specifically directed to nasal formulations. Instead, Aventis contends that a person of ordinary skill in the art is really a "team" of people: one with a pharmaceutical formulation background, specifically in thixotropic compositions and experience in using a Brookfield LVT viscometer, and one with medical training in the treatment of allergic rhinitis. (DX 320 at ¶¶ 7-9.)

[4] Aventis has no expert who is a pharmaceutical formulator or has designed pharmaceutical formulations. Its designated witness on ordinary skill is an allergic rhinitis expert.

260. This contention has no basis in fact or law. Aventis' position on the experience of the pharmaceutical formulator member of the "team" is backwards. Under their view, the formulator need not have *any* experience formulating nasal dosage forms, even though this is precisely the subject to which the patents are directed, but must have experience in thixotropic substances and a Brookfield LVT viscometer, which are merely the type of materials and instruments that the patents conclude can be used to effectively formulate the claimed nasal dosage forms.

261. While a pharmaceutical formulator of nasal dosage forms is likely to have experience with suspending agents in the course of his or her work, specific experience formulating thixotropic compositions and using a Brookfield LVT viscometer would not be required. These materials and instruments would be within the pharmaceutical formulator's skill even without the specific experience. Indeed, the Supreme Court made clear in *KSR* that the scope of the art is not limited to just the field of the person of ordinary skill: "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 127 S. Ct. at 1740. (FOF ¶¶ 101-105.)

262. Aventis' addition of a person with medical training in allergic rhinitis is similarly without merit. The problem the alleged invention is purporting to solve is not the treatment of allergic rhinitis; this was well known in the art. (FOF ¶¶ 101-105.) Rather, the invention purports to solve the problem of formulating a composition that will resist mucociliary clearance and retain the drug on the nasal mucosa – a problem for a pharmaceutical formulator, not a medical doctor. *Compare Daiichi*, 501 F.3d at 1257 (holding that person of skill in the art of

patent directed to *creating* a compound that would treat ear infections would be medically trained).

3. The Claimed Invention Was Obvious To Try And A Skilled Artisan Would Reasonably Expect It To Work.

263. Without question, the claimed invention here was "obvious to try" as *KSR* describes that concept. Each of the claim elements was disclosed in prior art products and references well within the technical grasp of a pharmaceutical formulator of nasal dosage forms.

a. A Skilled Artisan Would Be Motivated To Reformulate Nasacort Nasal Inhaler To The Claimed Aqueous Nasal Spray.

264. Under controlling case law, a claimed combination of prior art elements is obvious if the elements were known or within the technical grasp of the skilled artisan and he or she would reasonably expect the combination of elements to work. *KSR*, 127 S. Ct. at 1740; *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). While a motivation, teaching or suggestion to combine the elements is not required, it can be useful to demonstrate that the combination is obvious. *KSR*, 127 S. Ct. at 1741; *PharmaStem*, 491 F.3d at 1360. Absolute predictability of success is not required. Rather a reasonable expectation is sufficient. *Pfizer,* 480 F.3d at 1366.

265. Here, the formulator would have been motivated and readily able to convert Nasacort Nasal Inhaler to an aqueous nasal spray formulation, using the same dosing regimen as Nasacort Nasal Inhaler and containing the same excipients disclosed in already FDA-approved aqueous nasal sprays. Moreover, given the structural similarities of the active ingredients and the similarities of the Beconase AQ and Flonase formulations, the formulator would reasonably expect such a formulation to work for its intended purpose. (FOF ¶¶ 120-176.)

266. The impending ban on CFCs and the patient preference for an aqueous formulation, either alone or together, would also have motivated a person of ordinary skill to reformulate Nasacort Nasal Inhaler to an aqueous formulation, as would the disclosures in Settipane and Kobayashi. *See KSR*, 127 S. Ct. at 1741 ("[I]t often may be the case that market demand, rather than scientific literature, will drive design trends."). Thus the prior art would lead a formulator directly to the system claimed in the patents. *See KSR*, 127 S. Ct. at 1742 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."); *Pfizer*, 480 F.3d at 1354, 1366 (pre-*KSR*, holding that patent directed to specific salt form of compound, among 53 pharmaceutically acceptable anions, was obvious). (FOF ¶¶ 120-176.)

267. Apart from the active ingredient, the only substitutions for Nasacort AQ were to switch pheynylethyl alcohol to EDTA (FOF ¶¶ 6-29.) Both of these substitutions would have been routine to a pharmaceutical formulator of nasal sprays.

b. The Change From Phenylethyl Alcohol To EDTA Does Not Impart Novelty To The Asserted Claims.

268. First, EDTA had been used in numerous prior art nasal spray formulations, including formulations using glucocorticosteroids like Nasalide. It was known before July 3, 1995, for its synergistic antimicrobial effects when used with benzalkonium chloride, as well as its effectiveness in replacing antioxidants. (*See* FOF ¶¶ 130-133.) A skilled artisan also would have a motivation to use EDTA

– its proven synergistic antimicrobial effects with benzalkonium chloride and

known antioxidant properties. (DX34; DX48; Kim Tr. at 78:15-79:7; DX44; DX38; FOF ¶¶ 24-29.)

269. Replacing phenylethyl alcohol in the prior art formulations was therefore exactly the sort of simple substitution, assembling prior art teachings together "like pieces of a puzzle," that the Supreme Court found obvious in *KSR*. 127 S. Ct. at 1742, 1744-45 (holding patent obvious where it combined prior art directed to adjustable automobile pedal with a pivot mounted electronic sensor). *See also Leapfrog*, 485 F.3d at 1161 (affirming Court's obviousness decision in patent claiming combination of mechanical learning device with electronics).

270. In addition, Aventis cannot claim inventiveness of the use of EDTA based on '573 patent claim 5's "odorless" limitation, which is a readily apparent concern for nasal sprays. It was well known that EDTA was odorless while phenylethyl alcohol has a rose scent. (FOF ¶¶ 122-129.) *KSR*, 126 S. Ct. at 1740 ("[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result."); *Leapfrog*, 485 F.3d at 1162 (agreeing with this Court that a person of ordinary skill in the art would have found it obvious to combine mechanical learning toy with updated electronics to gain benefits of the adaptation).

271. Moreover, the obviousness of a claimed invention must be assessed on the basis of the properly construed claims. *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003). None of the three prior art aqueous formulations, Flonase, Beconase AQ or Vancenase AQ, contained an odor that causes the user discomfort. (FOF ¶¶ 122-129.) Therefore, under the claims as properly construed by the Court, each of these prior art compositions was "odorless."

272. Accordingly, both the substitution of EDTA for the phenylethyl alcohol in the prior art products and the resulting odorlessness would have been readily obvious to a person of ordinary skill in the art as of July 3, 1995.

c. The Change From One Claimed Suspending Agent To Another Does Not Impart Novelty To The Asserted Claims.

273. The simple change in suspending agent

likewise does not make Aventis' standard formulation patentable. While Aventis' two rheology experts, neither of whom is a pharmaceutical formulator, expressed "surprise" at the switch

, they ignore the fact that *both suspending agents fall squarely within the patent claims.* (FOF ¶¶ 120, 140-144.)

274. Moreover, it is simply "not inventive to discover the optimum or workable ranges by routine experimentation." *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997); *Pfizer*, 480 F.3d at 1368. That is *all* that Aventis is claiming.

(FOF ¶¶ 21-23; DX34; DX24; DX174.)

275. That routine testing is hardly sufficient to support a patentable invention under *KSR*. *See Pfizer*, 480 F.3d at 1366 ("[T]his is not the case where there are numerous parameters to try.").

276. Aventis attempts to dodge these facts by arguing that the claimed viscosity ranges imparted by the suspending agent – really only the shear viscosity range – are nonobvious. This, too, is wrong. As Dr. Klingenberg found, Flonase falls squarely within the claimed viscosity ranges, including the shear viscosity range. Therefore, it renders the claimed viscosity ranges

obvious. (FOF ¶¶ 136-139.) This fact defeats Aventis' claim to novelty or nonobviousness. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *EMI Group N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1351 (Fed. Cir. 2001).

277. Even if the prior art did not fall within the claimed shear viscosity range, Aventis cannot establish nonobviousness from what was merely routine optimization of the shear viscosity: "[T]he discovery of an optimum value of a variable in a known process is usually obvious." *Pfizer*, 480 F.3d at 1368; *accord Geisler*, 116 F.3d at 1470 (same); *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (same).

278. As noted, determining the appropriate shear viscosities required nothing more than routine optimization using the two known, commercially available suspending agents, Avicel RC-591 and Avicel CL-611. Nothing about the inventor's choice of Avicel CL-611 suggests that it alone would work in the claimed suspension, or that Avicel RC-591, despite falling squarely in the claimed concentration ranges, would not. J

A person of ordinary skill in the art would do exactly what the Nasacort AQ formulators did: test a spray pump while adjusting the concentrations of the two Avicel grades to determine the optimal concentration ranges that would produce the desired sprayability and suspendability characteristics. (*See, e.g.*, FOF ¶¶ 21-23.)

279. The patent specification even admits that optimization of the unsheared and shear viscosities would be routine:

> Suitable values for the setting viscosity and for the shear viscosity of the composition can be determined for a particular composition, taking into account also the particular means used to apply the composition to the nasal cavities.

('573 patent, col. 5:10-13.) This portion of the specification is a binding admission that the unsheared and shear viscosities can be determined through routine optimization. *See PharmaStem*, 491 F.3d at 1361-62 (holding that specification's statement that prior art disclosed claimed inventive feature was "binding on patentee for purposes of a later inquiry into obviousness"); *Sjolund v. Musland*, 847 F.2d 1573, 1577-79 (Fed. Cir. 1988).

280. And given this admission of routine optimization, which plainly seeks to establish enablement of the claims, Aventis cannot now avoid its binding effects in order to claim nonobviousness. *See Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1238 n.11 (Fed. Cir. 2008) (holding patentee to binding admission of routine optimization during patent prosecution for purposes of determining if prior art references were material); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988) (holding that patentee's admission during prosecution that substitutions could be made without undue experimentation was binding for purposes of obviousness).

281. To rebut this evidence Aventis has not offered testimony from a pharmaceutical formulator of any kind, let alone one who formulates nasal dosage forms. Instead, Aventis offers two rheology experts, neither of whom has designed a pharmaceutical formulation or nasal spray. Neither rheologist examines the prior art as a whole to determine whether the claimed invention would be obvious to a person of skill in the art.

282. Instead, one expert, Dr. Robert Prud'homme, argues that, from the perspective of a "rheologist of ordinary skill in the art," Avicel RC-591 would not "predict" the viscosity profile of Avicel CL-611 and that the two grades are not "interchangeable." (DX322 at ¶¶ 21-22.) As a factual matter, this simply is not true – both suspending agents were known in July 3, 1995 to be thixotropic. To the extent he is referring to the specific claimed shear range, this is

not the proper way to assess obviousness. Absolute predictability is not required, just a reasonable expectation of success. *Pfizer*, 480 F.3d at 1366. Indeed, Dr. Prud'homme's analysis of obviousness would obliterate the well-established rule that "it is not inventive to discover the optimum or workable ranges by routine experimentation." *Geisler*, 116 F.3d at 1470; *Pfizer*, 480 F.3d at 1368; *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) (holding invalid as obvious a claim to a titanium alloy reciting 0.8% nickel (Ni) and 0.3% molybdenum (Mo) when the prior art disclosed similar alloys having 0.75% Ni and 0.25% Mo as well as 0.94% Ni and 31% Mo); *In re Hill*, 284 F.2d 955, 959 (C.C.P.A. 1960) (affirming obviousness rejection of claim to chemical process conducted at 150-200 degrees when the prior art disclosed the same reaction at 300 degrees); *In re Aller*, 220 F.2d 454 (C.C.P.A. 1955) (affirming obviousness rejection of claim to chemical process reciting use of 25-70% sulfuric acid at 40-80 degrees when prior art disclosed same reaction with 10% sulfuric acid at 100 degrees).

283. Aventis' other rheology expert, Dr. Lochhead, quarrels with portions of prior art disclosures. (DX318.) He does not, however, deny that these prior art references disclose valuable information to a pharmaceutical formulator of nasal dosage forms about desirable excipients to use and characteristics to have in an aqueous nasal spray. (*See* FOF ¶¶ 106-119, 172-176.) Instead, he simply ignores how these references inform the prior art as a whole.

284. Dr. Lochhead's selective and piecemeal quibbles with portions of specific prior art disclosures is not the proper way to analyze obviousness. *See KSR*, 127 S. Ct. at 1742 ("The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the

same problem . . . . A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

285. Particularly when viewing the prior art knowledge as a whole, the use of commercially-available Avicel CL-611 in place of commercially-available RC-591 is a routine choice and, thus, exceedingly obvious to a skilled artisan as of July 3, 1995.

4. Secondary Considerations Do Not Rebut The Prima Facie Case Of Obviousness.

286. Aventis has asserted a number of secondary considerations to attempt to rebut the obviousness case. Aventis' evidence, however, does not meet the requirements for secondary considerations and is insufficient to rebut the strong prima facie case of obviousness.

a. Legal Standards For Secondary Considerations of Non-Obviousness.

287. "The rationale for giving weight to the so-called 'secondary considerations' is that they provide objective evidence of how the patented device is viewed in the marketplace, by those directly interested in the product." *Demaco Corp. v. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988) (citing *Graham*, 383 U.S. at 35-36). To establish secondary considerations of nonobviousness, "argument and conjecture are insufficient." *Id.* at 1393 (quotations and citation omitted). "These legal inferences or subtests . . . focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are the highly technical facts often present in patent litigation." *Graham*, 383 U.S. at 35-36.

288. To provide proper evidence of secondary considerations, a patentee must establish a nexus between the evidence presented and the merits of the claimed invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). The patentee bears the burden of demonstrating such

"a legally and factually sufficient connection." *In re Paulson*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

289. Moreover, secondary considerations "must be commensurate in scope with the claims which the evidence is offered to support." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003); *In re Clemens*, 622 F.2d 1029, 1035 (C.C.P.A. 1980). And secondary considerations are legally irrelevant to the extent they relate only to unclaimed features of a commercial embodiment. *In re Vamco Mach. & Tool, Inc.*, 752 F.2d 1564, 1577 (Fed. Cir. 1985).

290. Even when present, secondary considerations do not control the obviousness determination. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985). The evidence of secondary considerations must still be of sufficient weight to override a determination of obviousness based on primary considerations. Especially in light of *KSR*, "[c]ourts are reluctant to allow secondary factors to override a strong determination of obviousness based on primary considerations, even when all evidence relating to secondary factors is resolved in favor of plaintiff." *Anderson Corp. v. Pella Corp.*, 500 F. Supp. 2d 1192, 1197 (D. Minn. 2007).[5] Even *substantial* secondary indicia of non-obviousness will not save an obvious invention. *Leapfrog*, 485 F.3d at 1162 (substantial evidence of secondary considerations did not overcome finding of obviousness). *See also Pfizer*, 480 F.3d at 1372 (holding that unexpectedly superior results did "not overcome the strong showing of obviousness in this case").

[5] *See Apple Computer, Inc. v. Burst.com, Inc.*, No. C 06-0019, 2007 WL 3342829, at *5 n.1 (N.D. Cal. Nov. 8, 2007); *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 532 F. Supp. 2d 666 (D.N.J. 2007); *AdvanceMe Inc. v. RapidPay, LLC*, 509 F. Supp. 2d 593, 625 (E.D. Tex. 2007); *Asyst Techs., Inc. v. Empak, Inc.*, No. 98-20451, 2007 WL 2255220, at *8-9 (N.D. Cal. Aug. 3, 2007); *Friskit, Inc. v. RealNetworks, Inc.*, 499 F. Supp. 2d 1145, 1154 (N.D. Cal. 2007); *McNeil-PPC v. Perrigo Co.*, 576 F. Supp. 2d 238, 255 (S.D.N.Y. 2007).

b. The Claimed Invention Does Not Exhibit Unexpected Results.

291. Plaintiffs assert a number of "unexpected results" associated with the use of Nasacort AQ as secondary considerations. None meets the stringent proof required to establish an unexpected result under the law.

292. "This court and its predecessors have long held . . . that even though [a] modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges 'produce a new and unexpected result which is *different in kind and not merely in degree* from the results of the prior art.'" *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)) (emphasis added.)

293. Moreover, to establish unexpected results as evidence of non-obviousness, a patentee must present evidence that the results claimed to be unexpected *actually* occur. *See In re J.A.M.C. De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Indeed, speculation or unproven hypotheses about what might become an "unexpected result" simply is not enough. *Geisler*, 116 F.3d at 1469; *CFMT, Inc. v. YieldUp Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

i. The Claimed Invention Does Not Exhibit Unexpected Potency Results Compared With Flonase.

294. Aventis claims that it is unexpected that once-daily Nasacort AQ is clinically equivalent to once-daily Flonase, because the active component in Flonase (fluticasone propionate) is purportedly approximately nine times more potent than the active component in Nasacort AQ (TAA).

295. But there is absolutely nothing unexpected about the clinical efficacy of the claimed once daily dosing regimen of Nasacort AQ because the clinical efficacy of TAA was

already known given the Nasacort Nasal Inhaler and the Settipane and Kobayashi disclosures. Indeed, the Nasacort AQ formulators clearly expected this dosing regimen to work. (FOF ¶¶ 17-33, 42-43, 150-155.) Moreover, the efficacy of Nasacort AQ at the claimed once daily dosing was particularly unsurprising given that aerosol Beconase had previously been reformulated to Beconase AQ using the same dosing regimen for the active ingredient beclomethasone dipropionate. (FOF ¶ 155.)

296. Other than the bald assertions of their experts, none of whom is a pharmaceutical formulator, Aventis has failed to provide any factual evidence that it is an unexpected result that once-daily Nasacort AQ was clinically equivalent to once-daily Flonase. Such assertions do not constitute requisite factual evidence of unexpected results. *See Geisler*, 116 F.3d at 1469.

ii. The Claimed Invention Does Not Exhibit Unexpected Thixotropic Properties Compared With Flonase.

297. Aventis also argues that Nasacort AQ's viscosity profile provides unexpected results within the nasal cavity that are substantially different from those of Flonase.

298. But this argument is legally irrelevant because Flonase *has* the claimed viscosity profile and, thus, *is* within the scope of the claimed thixotropic profile. (FOF ¶¶ 136-139.) *See Peterson*, 315 F.3d at 1331; *Clemens*, 622 F.2d at 1035. Thus, arguments about "unexpected" advantage of the claimed profile are inapplicable to Flonase.

299. The argument is also based on a false premise. Even if Aventis were correct that Flonase falls outside the claimed shear viscosity range, Aventis has failed to prove either that the claimed invention exhibits unexpectedly better deposition or clearance than Flonase or that the supposed differences are due to the shear viscosity differences. Aventis' burden in this respect is heavy: Aventis must demonstrate that the purported difference was not just a difference in degree, but was a difference *in kind*. *Iron Grip*, 392 F.3d at 1322; *Huang*, 100 F.3d at 139.

Moreover, the showing must be made by objective, factual evidence. *See, e.g.*, *McNeil PPC, Inc. v. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) (rejecting evidence that clinical studies showed unexpected results because the clinical studies were "inconsistent, not shown to be reproducible, and did not include comparative data vis-à-vis placebos or other [similar products] necessary to demonstrate unexpected or synergistic effects").

300. Aventis does not have the requisite evidence.

FOF ¶¶ 147-149, 181-184.) Therefore, again, the so-called differences between the two products are legally irrelevant. *See Peterson*, 315 F.3d at 1331; *Clemens*, 622 F.2d at 1035.

301. Moreover, Aventis' assertions are factually unsupported.

302. Whatever opinion Dr. Berridge now has as a retained expert in this case,

which is the only basis on which a scientist can form a definite conclusion about the comparative deposition patterns of these products. (*See* Siegel Tr. at 10:10-11:1.)

303. Moreover, Aventis has not even attempted

Indeed, this difference could, in fact, be due to the spray device (Berridge 8/3/07 Tr. at 239:5-11) or even due to different clearance rates for the active ingredient itself. Accordingly, his musings about observational insignificant differences do not suffice to establish unexpected results. *See McNeil*, 337 F.3d at 1370 (rejecting evidence that clinical studies showed unexpected results because the clinical studies were "inconsistent, not shown to be reproducible, and did not include comparative data vis-à-vis placebos or other [similar products] necessary to demonstrate unexpected or synergistic effects"); *CFMT*, 349 F.3d at 1342; *Geisler*, 116 F.3d at 1469; *J.A.M.C. De Blauwe*, 736 F.2d at 705.

304. Finally,

is not a difference in kind, but merely a difference in degree. It is legally insufficient to establish any unexpected results. *Iron Grip*, 392 F.3d at 1322; *Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345-45 (Fed. Cir. 2006) (holding that it was understood in the art that side effects were linked to drug concentration in the blood and therefore it would be obvious to one of skill in the art that an extended release formulation would reduce side effects); *Huang*, 100 F.3d at 139 (holding that it was understood in the art that shock absorbing qualities of polyurethane

derived from compressible nature and it would be obvious that increasing thickness would increase shock absorption).

iii. The Claimed Invention Does Not Exhibit Any Other Unexpected Results.

305. Aventis argues that it is an unexpected result that patients rated Nasacort AQ as having significantly better taste and smell than twice-daily Beconase AQ.

306. First, taste is not a claimed feature of the invention, and therefore it is legally irrelevant. *See Vamco*, 752 F.2d at 1577. And there is insufficient evidence of a preference for the taste of Nasacort AQ in any event. (FOF ¶ 193.)

307. The only asserted independent claim which claims "odorlessness" is claim 5 of the '573 patent. As detailed above, Beconase AQ, as well as Flonase are odorless, within the meaning of the patent claims. (FOF ¶¶ 122-129.) But, even if either was not considered "odorless," there is nothing unexpected about the "odorless" qualities of Nasacort AQ. EDTA was known to be odorless and phenylethyl alcohol was known to have a rose scent. Again, having this knowledge, a pharmaceutical formulator would fully expect a product with EDTA and without phenylethyl alcohol to be odorless. *Baxter*, 952 F.2d at 392. (FOF ¶ 128.)

308. Aventis also claims that it is an unexpected result that the claimed invention's combination of a chelating agent and an anti-microbial agent provided resistance to oxidative degradation even absent inclusion of an antioxidant compound. This combination of a chelating agent and an anti-microbial agent providing an antioxidant effect is not a claimed feature of the invention, and is therefore legally irrelevant. *See Vamco*, 752 F.2d at 1577.

309. Moreover, this result would be entirely expected. EDTA was a known antioxidant in before July 3, 1995. (FOF ¶ 131.) Therefore, it cannot contribute to a finding of unexpected results. *Baxter*, 952 F.2d at 392.

310. To the extent that Aventis maintains its claim that the claimed "narrow" difference between the setting and shear viscosity provides an unexpected benefit, Dr. Lochhead has repudiated this opinion. He conceded that his opinion was limited to a difference of only 200 centipoise (which is the narrowest difference in the claims) and, thus, does not apply to the full scope of the claims (which cover differences as great as 750 centipoise). (FOF ¶¶ 185-187.) Thus, as a matter of law, this claimed unexpected result fails because it is not "commensurate in scope with the claims which the evidence is offered to support" as required by the Federal Circuit. *Peterson*, 315 F.3d at 1331; *Clemens*, 622 F.2d at 1035.[6]

311. Finally, if Aventis continues to assert that Nasacort AQ provided an unexpected benefit in terms of the treatment of eye symptoms, there is no evidence to support this claim. Aventis' own expert Dr. Kaliner conceded during his deposition that a number of intranasal steroid preparations, including Flonase, have been reported to improve eye symptoms. (FOF ¶¶ 188-189.) Again, Aventis has failed to meet its burden of providing factual evidence of an unexpected result. *See Geisler*, 116 F.3d at 1469-70.

c. The Claimed Invention Does Not Meet A Long-Felt, Unmet Need.

312. Aventis asserts that there was a long-felt need for an aqueous nasal spray that had the combination of properties of being odorless, resisting clearance, having uniform dosing through a pre-compression pump, and being safe and effective for adults and children via once-

[6] To the extent that Aventis attempts to revive its assertion that it is surprising that Nasacort AQ is a stable suspension despite the fact that it has a lower yield stress value, a more quickly diminished viscosity upon shearing, and a greater percentage of rapidly recovered viscosity following shearing, as compared to competitive products, Aventis has conceded this point as a matter of law by failing to provide any factual or expert evidence as required. *See Geisler*, 116 F.3d at 1469-70.

daily dosing administration. Aventis has not offered a single expert to testify as to the existence of this long-felt, unmet need, however.

313. In the context of drugs for use in human therapy, a "long-felt but unsolved need" is not present where there are already several other drugs of the same class in the marketplace. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, No. 2:05-CV-421, 2006 WL 2008962, at *45 (E.D. Va. July 17, 2006) (finding that there "simply was no 'long-felt need'" for a drug where there were already "several effective" drugs of the same class already on the market), *rev'd on other grounds*, 499 F.3d 1293 (Fed. Cir. 2007).

314. There was no long-felt need for the claimed invention, nor has Aventis supported its assertions with any evidence or testimony that there was. Quite the contrary, there were several effective drugs of the same class already on the market, including Beconase AQ, Vancenase AQ, and Flonase. Moreover, those drugs already had the properties for which Aventis claims there was a long-felt but unsolved need.

315. Each of these products were aqueous nasal sprays having uniform dosing. Each was approved as safe and effective in adults and Flonase was also effective in treating children and FDA approved for once daily dosing. There is no evidence that the other products in the class presented *any* problems with clearance to the throat or mouth. (FOF ¶ 181-184.) In addition, products such as Flonase, Beconase AQ, and Vancenase AQ were odorless, meaning that odors that cause the user discomfort are absent. (FOF ¶ 122-129, 190-194.)

316. In sum, not only were there several "effective" drugs of the same class already on the market, *Aventis Pharma*, 2006 WL 2008962 at *45, but at least one of those drugs – Flonase – had all of the attributes for which Aventis claims there was a long-felt need. Moreover, Aventis has not offered any expert testimony to prove that there was a long-felt, unmet need for a

nasal spray with all or any of these features. Instead, Aventis apparently is content to offer attorney argument and conclusory assertions, which is plainly insufficient under controlling Federal Circuit caselaw. *Demaco Corp.*, 851 F.2d at 1393 ("'[A]rgument' and 'conjecture' are insufficient.") (citations omitted).

d. There Is No Evidence That Others Tried, But Failed To Create The Claimed Invention.

317. Relying on the removal of Tri-Nasal Spray from the market, Aventis claims that competitors tried and failed to create an aqueous TAA steroid spray for the treatment of rhinitis that was odorless, resisted clearance to the throat and/or mouth, and was safe and effective for adults and children via once-daily dosing administration.

318. The "failure of others is probative only where the evidence shows that the prior failure occurred because 'the devices lacked the claimed features.'" *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006).[7]

319. Although Tri-Nasal Spray was an aqueous intranasal spray with TAA as its active ingredient, it was a co-solvent system that did not fall within the asserted patent claims. (FOF ¶ 97.) Aventis has presented no evidence that the formulators of Tri-Nasal Spray tried but failed to make the claimed aqueous formulation. Likewise, Aventis has presented no evidence that Tri-Nasal's recall from the market was due to the fact that Tri-Nasal lacked the "claimed features" of Nasacort AQ, as required by *Ormco Corp.* (FOF ¶¶ 196-198.)

320. Aventis therefore cannot meet its burden of proving that competitors tried and failed to overcome the problem Aventis claims to have solved as required by the Federal Circuit. *E.g.*, *Ormco Corp.*, 463 F.3d at 1313; *see also GPAC*, 57 F.3d at 1580 ("GPAC offers no

[7] Aventis cannot rely on the failure of Flonase, Beconase AQ or Vancenase AQ to achieve what Aventis contends are the benefits of Nasacort AQ for the reasons stated above. (*See supra*, ¶¶ 312-316.)

evidence that this inability or unwillingness of competitors to respond to [the] invention in the marketplace is rooted in the subject matter claimed in the [patent]. Accordingly, this secondary consideration can be accorded only little weight as evidence of nonobviousness.").

e. Aventis Cannot Establish A Nexus Between "Copying" And The Nonobviousness Of The Claimed Invention.

321. Aventis argues that a number of competitors, including Barr, copied Nasacort AQ. But Aventis cannot establish any nexus between the alleged copying and the nonobviousness of the claimed invention.

322. The deliberate copying of the patented invention may be evidence that the invention is non-obvious if there is some "nexus between [the] copying and the nonobviousness of the claimed invention." *Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1028 (Fed. Cir. 1985), *overruled on other grounds by Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356 (Fed. Cir. 1999). For example, copying is relevant "where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed." *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1196 (Fed. Cir. 2003) (quotations and citation omitted). But, "more than the mere fact of copying by an accused infringer is needed to make that action significant to a determination of the obviousness issue." *Cable Elec.*, 770 F.2d at 1028.

323. Evidence of an ANDA applicants' product development in ANDA cases is largely irrelevant to nonobviousness because the ANDA process effectively requires an ANDA applicant to copy the brand drug referenced in its ANDA. *See Aventis Pharma v. Lupin Ltd.*, 2006 WL 2008962, at *45; *Aventis Pharma Deutschland GmbH., v. Lupin Ltd.*, 403 F. Supp. 2d 484, 486 (E.D. Va. 2005); *Eli Lilly & Co. v. Teva Pharms., Inc.*, No. IP 02-0512-C-B/S, 2004 WL 1724632, at *38 n.21 (S.D. Ind. July 29, 2004).

324. The Hatch-Waxman Act requires ANDA applicants to demonstrate bioequivalence to the branded product to gain approval of their ANDA. 21 U.S.C. § 355(j)(2)(A)(iv). To establish bioequivalence for nasal sprays, FDA recommends that the ANDA product contain both the same active ingredient and the same inactive ingredients in essentially the same amounts as the branded drug. (FOF ¶ 48.) Thus, an ANDA applicant's "copying" of the branded drug is not competent evidence of deliberate copying of the patented invention. Simply put, the motivation for the "copying" exists not because of the patented invention but because of regulatory requirements.

325. And here, that is the uncontroverted evidence. Barr's ANDA product has a formulation that is qualitatively the same and quantitatively essentially the same as Nasacort AQ. But that is only because the FDA guidelines recommend such similarity for approval. (FOF ¶¶ 46-49.) These facts are uncontradicted. Aventis has not shown any nexus between Barr's copying and the alleged non-obviousness of its product. Accordingly, Aventis' argument fails. *Eli Lilly & Co.*, 2004 WL 1724632, at *38 n.21 ("[A defendant's] demonstration of equivalency to [the drug] to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention").

326. Aventis also argues that other competitive aqueous nasal products copied certain aspects of the asserted claims. Aventis claims that Nasonex was reformulated to eliminate phenylethyl alcohol to become odorless and that Veramyst copied characteristics of Nasacort AQ, including once-daily administration, odorlessness, and its inactive ingredients.

327. Aventis has presented no evidence of deliberate copying of Nasacort AQ by the formulators of Veramyst or the reformulators of Nasonex and no evidence of a nexus between the purported copying by Nasonex and Veramyst and the claimed features of Nasacort AQ as

required by the Federal Circuit. The bald assertions and speculation of Dr. Meltzer are simply insufficient. (FOF ¶¶ 199-201.) Therefore, Aventis has failed to meet its burden of demonstrating a nexus between copying and the claimed invention. *Demaco Corp.*, 851 F.2d at 1391.

f. Aventis Cannot Establish That Nasacort AQ Was A Commercial Success.

328. With respect to alleged commercial success, Aventis cannot meet its burden of showing that Nasacort AQ was a commercial success, or that any sales or prescriptions it achieved were due to the patented features.

329. For commercial success, a patentee must show a nexus between any such success and the patented attributes of the product. *Sandt Tech., Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001); *In re Paulson*, 30 F.3d 1475, 1482 (Fed. Cir. 1994); *Ashland Oil*, 776 F.2d at 306. Moreover, even a strong showing of commercial success may be insufficient, without more, to counter strong evidence of obviousness. *See Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 769 (Fed. Cir. 1988); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997); *McNeil*, 516 F. Supp. 2d at 254.

i. Aventis Has Not Established That Nasacort AQ Was Commercially Successful.

330. Aventis failed to prove that Nasacort AQ is a commercial success. It did not show that Nasacort AQ was cumulatively profitable, that it outperformed its market competitors or that it met any of Aventis' internal goals.

331. First, a commercial success showing is weak, at best, where the patentee fails to establish that the product was profitable. *See Cable Elec.*, 770 F.2d at 1026-27 ("Without further economic evidence . . . it would be improper to infer that the reported sales represent a

substantial share of any definable market or whether the profitability per unit is anything out of the ordinary in the industry involved."); *see Huang*, 100 F.3d at 137.

332. The ability to recoup developmental costs and provide the company with a cumulative profit is particularly significant when the commercial success of a pharmaceutical product is at issue. This is because of the high capital and correspondingly high risk involved in developing and commercializing a pharmaceutical product. (FOF ¶¶ 202.)

(FOF ¶¶ 203-204.)

333. Second, Nasacort AQ underperformed in comparison to its competitors. (FOF ¶¶ 205-206.) Nasacort AQ was never number one or even number two in sales or prescriptions during its lifetime. Aventis' argument that Nasacort AQ is a commercial success because it had "significant sales" fails. Sales levels, without more, do not support a finding of commercial success. *See Huang*, 100 F.3d at 140. (Bell Tr. at 226:16-227:17.) Moreover, Dr. Bell's opinion that Nasacort AQ had "significant sales" is fundamentally flawed. The IMS data upon which he relies does not provide actual net sales,

(FOF ¶ 204.)[8] Even if the IMS dollar sales data is considered, Nasacort AQ's dollar sales pale in comparison to Flonase and Nasonex, two of Nasacort AQ's key competitors. (FOF ¶ 205.)

334. Nasacort AQ has consistently underperformed in comparison to these more successful competitors, not only in sales dollars, but also in prescriptions and market share. Nasacort AQ has not kept pace with Flonase and Nasonex in total prescription growth. (FOF ¶

[8] Aventis' argument that price does not have any significant impact on the commercial success analysis is wrong. Nasacort AQ was less expensive than Flonase and Nasonex from 1996-2001, yet still failed to achieve the success of either of those two products. (FOF ¶ 209.)

205.) And, it has had a flat market share growth curve compared with Flonase and Nasonex over its life cycle. (FOF ¶ 205.)

335. In fact, the IMS data make clear that the market leader, Flonase, was responsible for the expansion in the INS market and buoyed the other competitors through its sales and marketing efforts. Therefore, any Nasacort AQ growth is attributable in large part to the overall growth of the INS market, driven primarily by Flonase. (FOF ¶ 205.) Nasacort AQ also did not demonstrate displacement of any of its competitors in the market, with the significant exception of Nasacort Nasal Inhaler. (FOF ¶ 205, 209); *see Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983) (explaining that evidence of commercial success includes "replacement of earlier units sold by others in dollar amounts").

336. Third, Nasacort AQ underperformed in view of the internal goals Aventis set for it. Another factor considered in determining whether a product is commercially successful is whether the product met the company's original internal expectations for its performance. *Emerson Elec. Co. v. Spartan Tool, LLC*, 223 F. Supp. 2d 856, 914 (N.D. Ohio 2002) (considering evidence that original sales expectations were exceeded).

337. When taken together, the evidence regarding Nasacort AQ's performance is, at best, extraordinarily weak evidence of commercial success. For these reasons, Aventis has failed to satisfy its burden of showing that Nasacort AQ was commercially successful.

ii. Aventis Has Not Established The Requisite Nexus Of Its Sales To The Patented Features.

338. Even assuming that Aventis made a sufficient showing that Nasacort AQ has been a commercial success, it has not met its burden of proving the requisite nexus between any such success and the purported patented features of the product.

339. Conclusory assertions are not sufficient to establish the prima facie case for a nexus between "commercial success" and the invention claimed in the patent. *Huang*, 100 F.3d at 140. The owner of the patent must provide factual, evidentiary support for the assertion of a nexus with, for example, "an affidavit from the purchaser explaining that the product was purchased due to the claimed features." *Id.* (requiring "proof that the sales were a direct result of the unique characteristics of the claimed invention"); *Paulson*, 30 F.3d at 1482 (to satisfy nexus requirement, patentee must establish "a legally and factually sufficient connection").

340. As an initial matter, Aventis' expert, Dr. Bell, bases his entire nexus opinion on a false premise: that "the benefits of Nasacort AQ include the nasal spray's thixotropic property, the lack of odor *and taste, and patient comfort.*" (DX312 at ¶ 4 (emphasis added).) While the patents claim thixotropy and complete lack of odor (neither of which is actually a patentable feature), they do not claim "taste" or "patient comfort," nor are any such benefits discussed anywhere in the patent specification. Because they are not claimed, they cannot form the basis for any nexus argument:

> Commercial success is relevant only if flows from the merits of the claimed invention. With regard to the [product at issue], all the evidence was to the effect that its commercial popularity was due to . . . a feature not claimed. Thus, the jury was not entitled to draw the inference that the success of these boards was due to the merits of the claimed invention.

Sjolund, 847 F.2d at 1582.

341. Therefore, even assuming Dr. Bell correctly identified two claimed features, thixotropy and odorlessness, his entire opinion is questionable because he did not conduct a separate analysis of the two claimed features from the unclaimed features for his nexus opinion. More fundamentally, Dr. Bell's opinion that Nasacort AQ's so-called success is tied to the alleged patented features of thixotropic and odorlessness is entirely conclusory and unsupported. At best, he bases his conclusion that there is a nexus on the fact that, in some years, Nasacort AQ sales increased over others. (FOF ¶ 214.) But the mere fact that there were sales does not establish a nexus. *Sjolund*, 847 F.2d at 1582 ("Nor could the [fact-finder], from the bare evidence of units sold and gross receipts, draw the inference that the popularity of the [sold units] was due to the merits of the invention.")

342. While testimonial evidence by customers expressing demand for a product and stating the reasons for the demand may support a nexus, Aventis submitted no such evidence by consumers. *See, e.g., Pro-Mold and Tool Co., Inc. v. Lakes Plastics, Inc.*, 75 F.3d 1568, 1574 (Fed. Cir. 1996) (finding affidavits by consumers stating product was "extremely popular" and "began selling rapidly and in large quantities as soon as it was introduced to the market" evidenced nonobviousness). Simply put, there is not a shred of evidence from consumers that they preferred Nasacort AQ to Flonase or Nasonex because Nasacort AQ is "thixotropic" or "odorless." To the contrary, the evidence shows that the INS market was undifferentiated and that Nasacort AQ failed to break through (

(FOF ¶¶ 211-215.)

343. Moreover, while Dr. Bell tries to tie the marketing of the product to what he says are the patented features, he has no factual evidence to back this up. The marketing messages were jumbled and usually adopted broad and ambiguous claims of "first line therapy," "patient

preferred," and "comfort." When a marketing message centered on thixotropy and odorlessness, it usually also included additional unclaimed features, such as taste. Therefore, there is no evidence that any of Nasacort AQ's sales can be attributed to marketing based on thixotropy or odorlessness. (FOF ¶¶ 213-215.)

344. More importantly, if patients actually preferred Nasacort AQ over Flonase, in any respect, Nasacort AQ should have performed better than Flonase, or at the very least, within striking distance. It did not. Rather Flonase and Nasonex, both outperformed it at a rate of 2 to 1 in total prescriptions. (FOF ¶ 205.)

345. In addition, there is substantial evidence that there were reasons other than the claimed features for the limited commercial success Nasacort AQ may have had. For instance, there is ample evidence that Nasacort AQ cannibalized sales from Nasacort Nasal Inhaler due to a preference for the active ingredient. (FOF ¶¶ 216-219.) *See McNeil*, 516 F. Supp. 2d at 254 (marketing plan that encouraged switching raised inference that product's purported success "derived at least in part from the cannibalization").

346. Another reason for Nasacort AQ sales was Aventis' general promotion of the product. Aventis extensively promoted Nasacort AQ. Even assuming there was some evidence that promotion of the purported patented features of thixotropy and odorlessness resulted in actual sales (there is none), the majority of this promotion was not directed to thixotropy and odorlessness. (FOF ¶¶ 220-221.) Therefore, Aventis cannot claim that its marketing efforts establish the requisite nexus. To the contrary, Aventis' promotional efforts prove that there is no nexus. *McNeil*, 516 F. Supp. 2d at 254. Accordingly, Aventis cannot meet the second requirement of commercial success either – the requirement that the alleged commercial success have a nexus to the claimed features of the product.

g. None Of The Secondary Considerations Evidence, Either Alone Or In Combination, Is Sufficient To Rebut The Strong Prima Facie Case Of Obviousness.

347. Finally, none of the evidence Aventis has on secondary considerations is sufficient to rebut the strong prima facie case of obviousness here. Indeed, Aventis or its experts have abandoned several of these secondary considerations. The remainder are legally insufficient. But even with substantial evidence of secondary considerations, they would be unable overcome the strong obviousness case here – which demonstrates that the claimed invention involved nothing more than simple substitution of functionally similar or even equivalent excipients. *Leapfrog*, 485 F.3d at 1162; *Pfizer*, 480 F.3d at 1372.

B. Aventis' Patents Are Invalid For Lack Of Enablement.

348. Aventis' patents are also invalid under Section 112 for a lack of enablement because they fail to give any clue about how to make a claimed composition that will deposit on the frontal sinus of an individual.

349. 35 U.S.C. § 112, ¶ 1 provides that the patent specification must describe "the manner and process of making and using [the claimed invention], . . . to enable any person skilled in the art . . . to make and use the [claimed invention.]" Thus, the enablement requirement is only satisfied "when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *Automotive Techs., Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1282 (Fed. Cir. 2007).

350. The Federal Circuit has made clear that the specification must enable "[t]he full scope of the claimed invention." *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008); *accord AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (holding

that full scope of patent claims directed to stainless steel coatings that claimed two types of aluminum, one of which did not work at the time of patent filing were not enabled.)

351. "[W]ith respect to enablement, the relevant inquiry lies in the relationship between the specification, the claims and the knowledge of one of ordinary skill in the art." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999). "If, by following the steps set forth in the specification, one of ordinary skill in the art is not able to replicate the claimed invention without undue experimentation, the claim has not been enabled as required by § 112, paragraph 1." *Id.*

352. As this Court has properly construed the asserted claims of the '573 and '329 patents, the full scope of the asserted claims includes a requirement that the TAA in the claimed composition must deposit on the frontal sinus. Several claims further require portions of the TAA to remain on the frontal sinus for at least about an hour.

353. But the patent contains only one formulation example – Nasacort AQ as described in Example 1 – which does *not* reach the frontal sinus. ('573 patent, col. 9:5-25; DX25; FOF ¶¶ 75-100.)

354. This fact alone demonstrates that Aventis' patents are not enabled: "If an inventor attempts but fails to enable his invention in a commercial product that purports to be an embodiment of the patented invention, that is strong evidence that the patent specification lacks enablement." *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1319 (Fed. Cir. 2007) (affirming finding of lack of enablement of patent directed to orthodontic device based on inventors' inability to make claimed device that would overcome variations in human anatomy); *Liebel-*

Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1379 (Fed. Cir. 2007) (affirming lack of enablement of patents where inventors were unable to produce part of claimed invention).

355. Moreover, given the inherent anatomical obstacles to the frontal sinus, it is difficult to see how anyone of skill in the art could formulate the claimed nasal spray formulation that reaches the frontal sinus without undue experimentation. (FOF ¶¶ 75-100.)

356. In sum, "by following the steps set forth in the specification, one of ordinary skill in the art is not able to replicate the claimed invention without undue experimentation" because such a person would not be able to formulate a nasal spray that reaches the frontal sinus. *Nat'l Recovery*, 166 F.3d at 1196 (affirming lack of enablement because specification only enabled skilled artisan to approximate claims). Thus, the patents are invalid for lack of enablement.

C. Plaintiffs' Prior Public Use Of Nasacort AQ Renders The Patents In Suit Invalid.

357. A patent is invalid if the invention was "in public use . . . in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Whether a patent is invalid due to a § 102(b) public use is a question of law based on the underlying facts. *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002). A public use "includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor." *Id.* (internal quotations omitted); *see also Egbert v. Lippmann*, 104 U.S. 333, 336 (1881). Public use can occur even if the invention itself cannot be discerned by an observer and even if the use and knowledge of the use are confined to one person. *Baxter Int'l Inc. v. COBE Labs. Inc.*, 88 F.3d 1054, 1058 (Fed. Cir. 1996).

1. The Settipane And Kobayashi Studies Were Invalidating Prior Public Uses Of Nasacort AQ.

358. The Settipane and Kobayashi studies constitute invalidating public uses

Netscape, 295 F.3d at 1320. (FOF ¶¶ 37-40.)

359. There is no question that

360. For an invention to escape the § 102(b) statutory bar, the inventor must maintain supervision and control of the invention in the pre-critical date period. *See Lough v. Brunswick Corp.*, 86 F.3d 1113, 1121 (Fed. Cir. 1996). The use of an invention is public if the inventor does not retain control of the public's use of the invention and dissemination of information about the invention. *See Baxter*, 88 F.3d at 1058-59; *Beachcombers, Int'l Inc. v. WildeWood Creative Prods. Inc.*, 31 F.3d 1154, 1160 (Fed. Cir. 1994). Indeed, even a *single* use of an invention by a *single* third party, even if the invention is not discernable to a mere observer, will be a public use unless the inventor exercises adequate control over the use by the third party. *Egbert*, 104 U.S. at 336.

361.

See In re Hamilton, 882 F.2d 1576,

1581-83 (Fed. Cir. 1989) (holding that lack of involvement by inventor in alleged testing is an important factor in determining that use was not experimental); *MSM Invs. Co., L.L.C. v. Carolwood Corp.*, 70 F. Supp. 2d 1044, 1053 (N.D. Cal. 1999) (holding that defendant established a prima facie case of public use in part by providing evidence that the named inventor did not control administration of the invention).

362.

Therefore,

the most critical aspect of control was lacking

Compare Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820, 912 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006) (Lilly employees administered the study drug to patients who remained in the research ward for the duration of the study).

363.

This is another significant factor in determining whether the studies trigger the § 102(b) public use statutory bar. *Netscape*, 295 F.3d at 1320-21; *Baxter*, 88 F.3d at 1058-59; *MSM Invs.*, 70 F. Supp. 2d at 1053. As noted above, "[t]he statutory phrase 'public use' does not necessarily mean open and visible in the ordinary sense; it includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or *obligation of secrecy* to the inventor." *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1297 (Fed. Cir. 2002) (emphasis added).

Confidentiality obligations must be imposed on those that use or observe the invention. Confidentiality is established through evidence of either formal, signed confidentiality agreements between the parties or through an informal understanding of the confidential nature of the use. *See, e.g.*, *Netscape*, 295 F.3d at 1323 (holding that the inventor's failure to impose confidentiality agreements on those who used the invention placed the invention in public use); *MSM Invs.*, 70 F. Supp. 2d at 1053 (finding public use in part because the human patients to which the test drug was administered were not bound by any type of confidentiality agreement with the inventor or doctors); *Baxter*, 88 F.3d at 1059 (holding that the "lack of effort to maintain the [invention] as confidential coupled with the free flow into [the] laboratory of people . . . who observed the [invention] in operation and who were under no duty of confidentiality supports only one conclusion: that the [invention] was in public use").

364. Here,

New Railhead, 298 F.3d at 1297. (FOF ¶¶ 39-40.)

Netscape, 295 F.3d at 1321 (finding that the inventor "did not make any discernable effort to inform the 1991 demonstration attendees of the requirement of confidentiality, or otherwise indicate to them that they would owe him a duty of confidentiality").

365.

is not sufficient to establish confidentiality of the use.

366. Moreover, tl

does not make its use non-public. In *New Railhead*, for instance, the Federal Circuit concluded that use of a patented drill bit underground and out of public view was nevertheless a public use because "it is not public knowledge of [the] invention that precludes the inventor from obtaining a patent for it, but a public use or sale of it." 298 F.3d at 1299 (citations and quotations omitted).

367. Therefore, Kim's and Aventis' failure to secure the confidentiality of the patient use of Nasacort AQ during the Settipane and Kobayashi studies placed the invention in public use. *Compare Netscape*, 295 F.3d at 1321, *MSM Invs.*, 70 F. Supp. 2d at 1053, *with Eli Lilly*, 364 F. Supp. 2d at 912.

2. Plaintiffs Can Advance No Argument To Avoid The Public Use Statutory Bar.

368. Aventis has tried to, but cannot, establish experimental use to avoid the § 102(b) statutory bar. That exception applies only *before* reduction to practice,

369. "A patentee may negate a showing of public use by coming forward with evidence that its use of the invention was experimental." *Lough*, 86 F.3d at 1120. The experimental use doctrine was created to provide an inventor time to "complet[e] an invention to

the point of determining that it will work for its intended purpose," that is, to reduce the invention to practice. *RCA Corp. v. Data Gen. Corp.*, 887 F.2d 1056, 1061 (Fed. Cir. 1989).

370. The protection afforded by the experimental use doctrine expires, however, the moment an invention is reduced to practice. *New Railhead*, 298 F.3d at 1297; *Lough*, 86 F.3d at 1120; *RCA Corp.*, 887 F.2d at 1061. Reduction to practice of a pharmaceutical composition occurs when the inventor "actually prepared the composition and knew that it would work." *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 592 (Fed. Cir. 1997) (internal quotations omitted). Therefore, uses of the claimed invention after it was reduced to practice cannot be "experimental" as a matter of law.

371. Moreover, an invention can be "reduced to practice" for the purpose of the § 102(b) statutory bar even though it is not commercially perfected and may later be improved or refined. *New Railhead*, 298 F.3d at 1297; *In re Anthony*, 414 F.2d 1383, 1396 (C.C.P.A. 1969). "There is no requirement that an invention function perfectly in order to be reduced to practice or considered as on sale or in public use." *Harrington Mfg. Co., Inc. v. Powell Mfg. Co.*, 815 F.2d 1478, 1481 (Fed. Cir. 1986); *E. Rotorcraft. Corp. v. United States*, 384 F.2d 429, 431 (Ct. Cl. 1967).

372. Similarly, reduction to practice from a patentability standpoint is in no way contingent on what the FDA requires of applicants. Clinical trials approved by the FDA are not *per se* experimental uses. "[T]o allow federal regulatory laws to control the patent law meaning of 'public use' or 'on sale' would result in a haphazard operation of the Patent Office . . . A use or sale labeled 'experimental' by a government regulatory agency is not necessarily 'experimental' under the patent laws. As stated before, a claimed invention may be complete under the patent law while remaining experimental in the regulatory sense." *Pennwalt Corp. v.*

Akzona Inc., 570 F. Supp. 1097, 1107 (D. Del. 1983), *aff'd*, 740 F.2d 1573 (Fed. Cir. 1984). Accordingly, "approval by [the FDA] is not a prerequisite for the patenting of a new drug . . . the FDA need not necessarily determine that a drug is commercially useful or usable before it may be 'useful' in the patent sense." *In re Anthony*, 414 F.2d at 1393, 1395; *Scott v. Finney*, 34 F.3d 1058, 1063-64 (Fed. Cir. 1994).

373.

That alone ends the analysis.

374. But there are also other reasons to conclude that Nasacort AQ was reduced to practice prior to the clinical trials.

Nasacort AQ's dosing regimen mimicked Nasacort Nasal Inhaler. (FOF ¶¶ 31-33.)

Aventis knew Nasacort AQ would work for its intended purpose before it conducted the clinical trials. Because Aventis knew that it would work for its intended purpose prior to the Settipane and Kobayashi studies, Nasacort AQ was reduced to practice, even if it still required testing to satisfy FDA regulatory requirements. *Scott*, 34 F.3d at 1063-64. Accordingly, the Settipane and Kobayashi studies could not have been experimental uses excepted from the § 102(b) statutory bar.

375. Finally, even if Aventis could present evidence that Nasacort AQ was not reduced to practice prior to the Kobayashi study from December 1992 to March 1993, the Settipane study remains an invalidating public use. The Kobayashi study proved that Nasacort AQ is safe and

effective to treat perennial allergic rhinitis. (FOF ¶¶ 41-42.) Therefore, Aventis knew that Nasacort AQ worked for its intended purpose of treating perennial allergic rhinitis. At this point, Aventis also knew that Nasacort AQ was safe and effective for the treatment of seasonal allergic rhinitis, well before the Settipane study occurred: "Yes. So if you ask me if a product worked for PAR [perennial allergic rhinitis], should I anticipate it would work for SAR [seasonal allergic rhinitis], and the answer is I should anticipate that." (Kaliner Tr. at 191:6-9.)

376.

Accordingly, Nasacort AQ was also reduced to practice for allergic rhinitis: . At a minimum, the Settipane study was not an experimental use as a matter of law, but rather an invalidating prior public use in violation of § 102(b) of the Patent Act.

CONCLUSION

For all of the reasons set forth above, Barr is entitled to a judgment of noninfringement and patent invalidity.

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on April 14, 2008, I caused to be electronically filed a true and correct copy of the foregoing redacted document, ***Defendant Barr Laboratories, Inc.'s Proposed Findings of Fact and Conclusions of Law***, with the Clerk of the Court using CM/ECF, which will send notification of such filing to the following counsel of record:

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